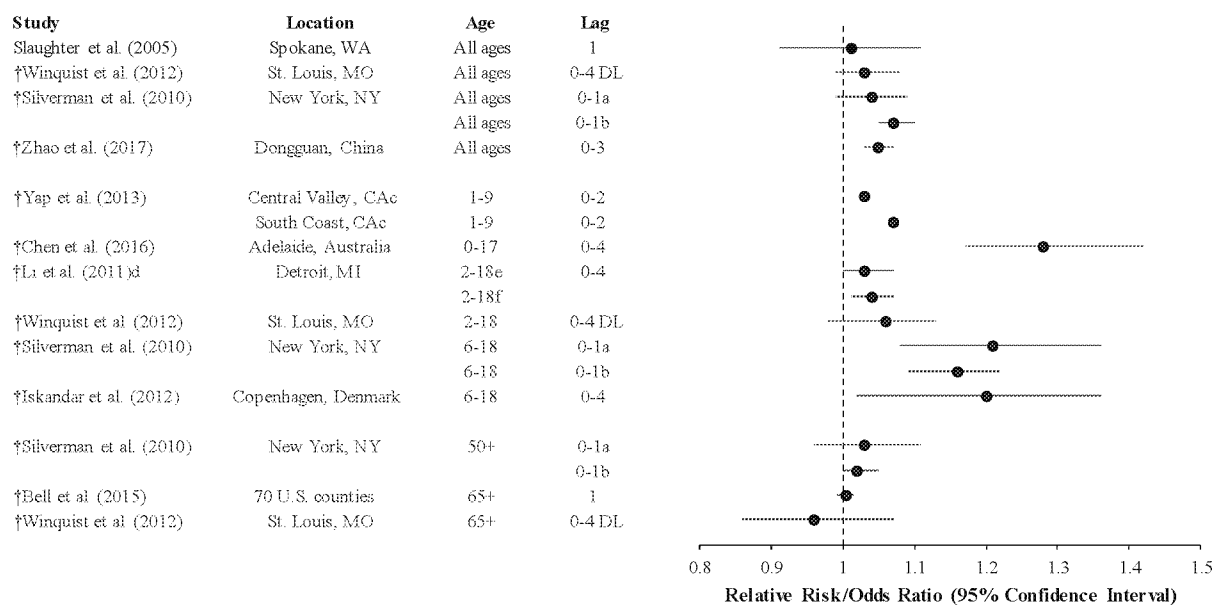


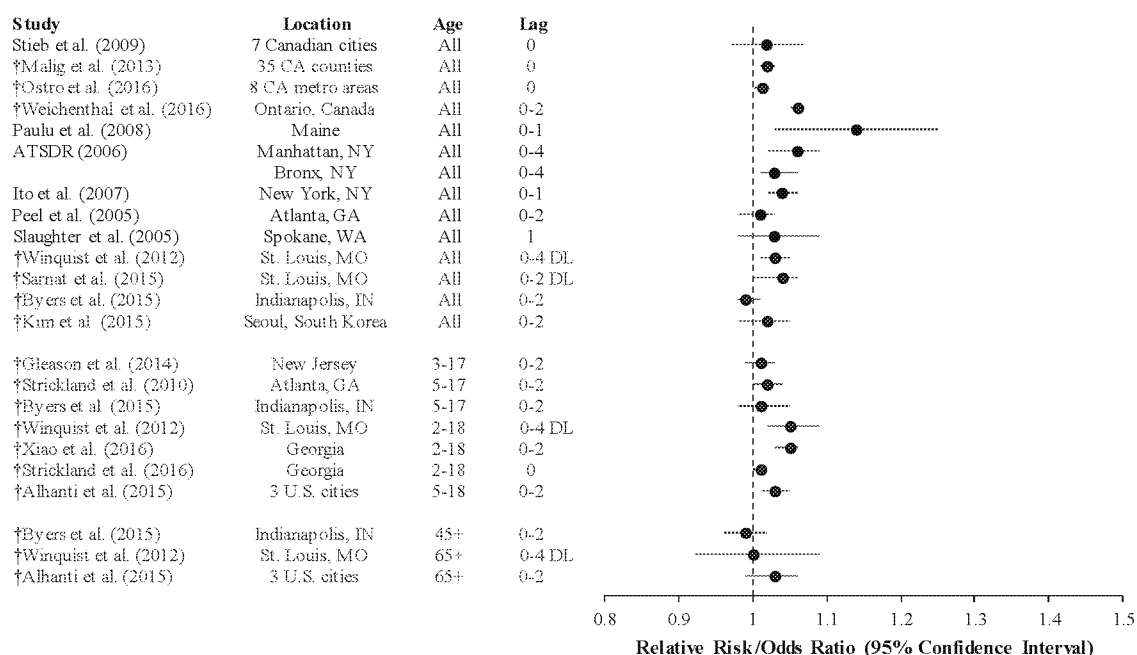
1 section, Table 5-1 presents the air quality characteristics of each city, or across all cities, the exposure  
2 assignment approach used, and information on copollutants examined in each asthma hospital admission  
3 and ED visit study. Other recent studies of asthma hospital admissions and ED visits are not the focus of  
4 this evaluation because they did not address uncertainties and limitations in the evidence previously  
5 identified, and therefore, do not directly inform the discussion of policy-relevant considerations detailed  
6 in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed  
7 a short study duration, or had insufficient sample size. The full list of these studies can be found here:  
8 (<https://hero.epa.gov/hero/particulate-matter>).

9         Recent studies expand the evidence base from the 2009 PM ISA (U.S. EPA, 2009) with respect to  
10 the evaluation of asthma hospital admissions and further reinforce the results reported in studies that  
11 examined asthma ED visits. As summarized in Figure 5-2- and Figure 5-3, both studies of hospital  
12 admissions and ED visits report evidence of consistent positive associations when examining children and  
13 people of all ages, with inconsistent evidence of associations with short-term PM<sub>2.5</sub> exposure for older  
14 adults (i.e., generally >65 years of age). These results are further supported by meta-analyses that include  
15 studies reviewed in and published since the 2009 PM ISA (Fan et al., 2015; Zheng et al., 2015). The  
16 results from asthma hospital admission and ED visit studies are supported by a study focusing on asthma  
17 physician visits in Atlanta, for the initial time period of the study, but this pattern of associations was not  
18 observed for the later time period (Sinclair et al., 2010). However, it is important to note that the severity  
19 of a PM<sub>2.5</sub>-related asthma exacerbation, personal behavior such as delaying a visit to the doctor for less  
20 severe symptoms, and insurance type (i.e., physician visits which often are ascertained for members of a  
21 managed care organization) may dictate whether an individual visits the doctor or a hospital, making it  
22 difficult to readily compare results between studies focusing on physician visits versus hospital  
23 admissions and ED visits.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. a = Intensive Care Unit (ICU) hospital admissions; b = non-ICU hospital admissions; c = values of confidence intervals not reported, but above the null; d = combination of hospital admissions and ED visits; e = time-series model results; f = case-crossover model results. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-2 Summary of associations between short-term PM<sub>2.5</sub> exposures and asthma hospital admissions for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. DL = distributed lag. Corresponding quantitative results are reported in Supplemental Material ([U.S. EPA, 2018](#)).

**Figure 5-3 Summary of associations from studies of short-term PM<sub>2.5</sub> exposures and asthma emergency department (ED) visits for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

**Table 5-1 Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range   | Exposure Assessment   | Mean Concentration<br>µg/m <sup>3a</sup>                                    | Upper Percentile<br>Concentrations µg/m <sup>3a</sup>                           | Copollutant<br>Examination  |
|---|---|---|---|---|
| <b>Hospital admissions</b>  |   |   |   |   |
| † <a href="#">Yap et al. (2013)</a><br>12 counties, Central Valley and South Coast, CA<br>2000–2005<br>1–9 yr           | Average of all monitors in<br>each county                                     | 12.8–24.6   | NR  | Correlation (r):<br>NA<br>Copollutant<br>models with: NA                              |
| † <a href="#">Bell et al. (2015)</a><br>213 U.S. counties<br>1999–2010<br>≥65 yr  | Average of all monitors in<br>each county                                     | U.S.: 12.3<br>Northeast: 12.0<br>Midwest: 12.9<br>South: 12.4<br>West: 11.3 | Max U.S.: 20.2<br>Northeast: 16.4<br>Midwest: 16.5<br>South: 16.5<br>West: 20.2 | Correlation (r):<br>NA<br>Copollutant<br>models with: NA                              |
| † <a href="#">Hebborn and Cakmak (2015)</a><br>10 Canadian cities<br>1994–1997<br>All ages                              | Average of all monitors in<br>each city                                       | 2.6–21.4  | NR  | Correlation (r):<br>NA<br>Copollutant<br>models with:<br>Pollen                       |
| † <a href="#">Silverman and Ito (2010)</a><br>New York, NY<br>1999–2006 (warm season only)<br>All ages, 6–18 yr, ≥50 yr | Average of 24 monitors  | 13 <sup>b</sup>   | 75th: 21<br>90th: 29  | Correlation (r):<br>0.59 O <sub>3</sub><br>Copollutant<br>models with: O <sub>3</sub> |
| † <a href="#">Liu et al. (2016)</a><br>Greater Houston area, TX<br>2008–2013<br>All ages                                | Average of four monitors<br>in one county, study area<br>covers nine counties | 12.0  | 90th: 18.5  | Correlation (r):<br>NA<br>Copollutant<br>models with: NA                              |

**Table 5-1 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range                                      | Exposure Assessment    | Mean Concentration<br>µg/m <sup>3a</sup> | Upper Percentile<br>Concentrations µg/m <sup>3a</sup> | Copollutant<br>Examination   |
|--|------------------------|--|---|--|
| †Kim et al. (2012)<br>Denver, CO<br>2003–2007<br>All ages              | One monitor            | 7.9                                      | Max: 59.4   | Correlation (r):<br>0.46 EC, 0.54,<br>OC, 0.68 SO <sub>4</sub> ,<br>0.82, NO <sub>3</sub><br><br>Copollutant<br>models with: NA  |
| †Iskandar et al. (2012)<br>Copenhagen, Denmark<br>2001–2008<br>0–18 yr | One monitor            | 10.3                                     | 75th: 11.8  | Correlation (r):<br>0.33 NO <sub>2</sub> , 0.33<br>NO <sub>x</sub> , 0.85 PM <sub>10</sub> ,<br>0.26 UFP<br><br>Copollutant<br>models with:<br>NO <sub>2</sub> , NO <sub>x</sub> , UFP   |
| †Chen et al. (2016)<br>Adelaide, Australia<br>2003–2013<br>0–17 yr     | One monitor            | 7.8                                      | 75th: 9.1<br>Max: 61.2                                | Correlation (r):<br>NA<br><br>Copollutant<br>models with: NA   |
| †Cheng et al. (2015)<br>Kaohshing, Taiwan<br>2006–2010<br>All ages     | Six monitors averaged  | 45.9                                     | 75th: 61.9<br>Max: 144                                | Correlation (r):<br>0.69 PM <sub>10–2.5</sub> ,<br>0.40 O <sub>3</sub> , 0.67<br>NO <sub>2</sub> , 0.69 SO <sub>2</sub><br><br>Copollutant<br>models with: O <sub>3</sub> ,<br>NO <sub>2</sub> , CO, SO <sub>2</sub><br>(but all stratified<br>by temperature) |
| †Zhao et al. (2016)<br>Dongguan, China<br>2013–2015<br>All ages        | Five monitors averaged | 42.6                                     | 75th: 56.8<br>Max: 192.7                              | Correlation (r):<br>0.42 O <sub>3</sub> , 0.80<br>NO <sub>2</sub> , 0.81 CO,<br>0.25 SO <sub>2</sub><br><br>Copollutant<br>models with: O <sub>3</sub> ,<br>NO <sub>2</sub> , SO <sub>2</sub>  |

**Table 5-1 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range  | Exposure Assessment   | Mean Concentration<br>µg/m <sup>3a</sup>  | Upper Percentile<br>Concentrations µg/m <sup>3a</sup>   | Copollutant<br>Examination  |
|--|---|---|---|---|
| <b>ED visits</b>   |   |   |   |   |
| <u>ATSDR (2006)</u><br>Manhattan and Bronx, NY<br>1999–2000<br>All ages                            | One monitor per borough   | 24-h avg<br>Manhattan: 16.7<br>Bronx: 15.0<br>1-h max<br>Manhattan: 27.6<br>Bronx: 27.6         | NR  | Correlation (r):<br>Bronx<br>24-h avg: 0.19<br>O <sub>3</sub> , 0.61 NO <sub>2</sub> ,<br>0.45 SO <sub>2</sub> , 0.19<br>pollen, 0.32 mold<br>1-h max: 0.35<br>O <sub>3</sub> , 0.55 NO <sub>2</sub> ,<br>0.28 SO <sub>2</sub><br>Copollutant<br>models with: O <sub>3</sub> ,<br>NO <sub>2</sub> , SO <sub>2</sub> |
| <u>Ito et al. (2007)</u><br>New York, NY<br>1999–2002<br>All ages                                  | Average of 30 monitors  | 15.1  | 75th: 19<br>95th: 32  | Correlation (r):<br>NA<br>Copollutant<br>models with: O <sub>3</sub> ,<br>NO <sub>2</sub> , CO, SO <sub>2</sub>   |
| <u>Peel et al. (2005)</u><br>Atlanta, GA<br>1998–2000<br>All ages                                  | One monitor   | 19.2  | 90th: 32.3  | Correlation (r):<br>NA<br>Copollutant<br>models with: NA  |
| <u>Stieb et al. (2009)</u><br>Seven Canadian cities<br>1992–2003, varies across cities<br>All ages | One monitor to average of<br>seven<br>One monitor Halifax,<br>Ottawa, Vancouver.<br>Three Edmonton. Seven<br>Montreal, Toronto. | Halifax: 9.8<br>Montreal: 8.6<br>Toronto: 9.1<br>Ottawa: 6.7<br>Edmonton: 8.5<br>Vancouver: 6.8 | 75th, Halifax: 11.3<br>Montreal: 10.9<br>Toronto: 11.9<br>Ottawa: 8.7<br>Edmonton: 10.9<br>Vancouver: 8.5 | No copollutant<br>model<br>$r = -0.05$ to 0.62<br>O <sub>3</sub> , 0.27–0.51<br>NO <sub>2</sub> , 0.01–0.42<br>CO, 0.01–0.55<br>SO <sub>2</sub>   |

**Table 5-1 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range   | Exposure Assessment  | Mean Concentration<br>µg/m <sup>3a</sup>                             | Upper Percentile<br>Concentrations µg/m <sup>3a</sup> | Copollutant<br>Examination   |
|---|--|--|---|--|
| <u>Paulu and Smith (2008)</u><br>Maine, whole state<br>2000–2003 (warm season only)<br>All ages | Kriging of monitors<br>Estimates for zip code<br>centroid. Number<br>monitors and method<br>validation NR.         | 8–9 <sup>b</sup>   | Max across yr: 20 in 2000<br>to 42 in 2003            | Does not persist<br>with: O <sub>3</sub><br><i>r</i> across<br>yr = 0.76–0.87<br>O <sub>3</sub>  |
| <u>†Alhanti et al. (2016)</u><br>Three U.S. cities<br>1993–2009<br>5–18 yr, ≥65 yr              | One monitor in each city   | Atlanta: 14.1<br>St. Louis: 13.6<br>Dallas: 11.1                     | NR  | Correlation ( <i>r</i> ):<br>0.57 O <sub>3</sub> , 0.39<br>NO <sub>2</sub> Atlanta; 0.42<br>O <sub>3</sub> , –0.15 NO <sub>2</sub><br>Dallas; 0.29 O <sub>3</sub> ,<br>0.29 NO <sub>2</sub> St.<br>Louis<br>Copollutant<br>models with: NA |
| <u>†Krall et al. (2016)</u><br>Four U.S. cities<br>1999–2010<br>All ages                        | One monitor in each city   | Atlanta: 15.6<br>St. Louis: 13.6<br>Dallas: 10.7<br>Birmingham: 17.0 | NR  | Correlation ( <i>r</i> ):<br>NA<br>Copollutant<br>models with: NA  |
| <u>†Malig et al. (2013)</u><br>35 California counties<br>2005–2008<br>All ages                  | Nearest monitor within<br>20 km from population-<br>weighted centroid of each<br>patient's residential zip<br>code | 5.2–19.8   | NR  | Correlation ( <i>r</i> ):<br>NA<br>Copollutant<br>models with:<br>PM <sub>10–2.5</sub>   |
| <u>†Ostro et al. (2016)</u><br>2005–2009<br>Eight California metro areas<br>All ages            | Nearest monitor within<br>20 km from population-<br>weighted centroid of each<br>patient's residential zip<br>code | 16.5   | NR  | Correlation ( <i>r</i> ):<br>NA<br>Copollutant<br>models with: NA  |

**Table 5-1 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range   | Exposure Assessment  | Mean Concentration<br>µg/m <sup>3a</sup> | Upper Percentile<br>Concentrations µg/m <sup>3a</sup> | Copollutant<br>Examination   |
|---|--|--|---|--|
| † <a href="#">Xiao et al. (2016)</a><br>Georgia<br>2002–2008<br>2–18 yr                                       | Combination of CMAQ model estimates and ground-based measurements at 12-km grid cells as detailed in <a href="#">Friberg et al. (2016)</a> ; 10-fold cross validation, 76%; grid cells averaged over each zip code | 13.2                                     | 75th: 16.1<br>Max: 86.4                               | Correlation (r):<br>0.61 O <sub>3</sub> , 0.22 NO <sub>2</sub> , 0.26 CO,<br>0.21 SO <sub>2</sub><br>Copollutant models with: NA |
| † <a href="#">Strickland et al. (2015)</a><br>Georgia<br>2002–2010<br>2–18 yr                                 | Satellite aerosol optical depth measurements at 1-km as detailed in <a href="#">Hu et al. (2014)</a> ; R <sup>2</sup> ranged from 0.71 = 0.85; grid cells averaged over each zip code                              | 12.9 <sup>b</sup>                        | 75th: 17.4<br>99th: 37.4                              | Correlation (r):<br>NA<br>Copollutant models with: NA  |
| † <a href="#">Gleason et al. (2014)</a><br>New Jersey, whole state<br>2004–2007 (warm season only)<br>3–17 yr | Fuse-CMAQ at 12-km grid cells assigned to geocoded address   | NR                                       | Max: 47.2   | Correlation (r):<br><0.34 pollens,<br>0.56 O <sub>3</sub><br>Copollutant models with:<br>Pollen                                  |
| † <a href="#">Weichenthal et al. (2016)</a><br>Ontario, Canada (15 cities)<br>2004–2011<br>All ages           | Nearest monitor to population-weighted zip code centroid or single available monitor   | 7.1                                      | Max: 56.8   | Correlation (r):<br><0.42 NO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> , NO <sub>2</sub> , oxidative potential     |

**Table 5-1 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range   | Exposure Assessment                            | Mean Concentration<br>µg/m <sup>3a</sup> | Upper Percentile<br>Concentrations µg/m <sup>3a</sup> | Copollutant<br>Examination   |
|---|--|--|---|--|
| † <a href="#">Strickland et al. (2010)</a><br>1993–2004<br>Atlanta, GA<br>5–17 yr                   | Population-weighted<br>average across monitors | 16.4                                     | NR  | Correlation (r):<br>Warm<br>season = 0.50<br>O <sub>3</sub> , 0.36 NO <sub>2</sub> ,<br>0.32 CO, 0.13<br>SO <sub>2</sub> ; cold<br>season = –0.12<br>O <sub>3</sub> , 0.37 NO <sub>2</sub> ,<br>0.38 CO, 0.00<br>SO <sub>2</sub> .<br>Copollutant<br>models with: NA |
| † <a href="#">Sarnat et al. (2015)</a><br>St. Louis, MO<br>2001–2003<br>All ages                    | One monitor                                    | 18.0                                     | NR  | Correlation (r):<br>0.25 CO, 0.35<br>NO <sub>2</sub> , 0.08 SO <sub>2</sub> ,<br>0.23 O <sub>3</sub><br>Copollutant<br>models with: NA   |
| † <a href="#">Byers et al. (2015)</a><br>Indianapolis, IN<br>2007–2011<br>All ages, 5–17 yr, ≥45 yr | Average of three monitors                      | 13.4                                     | NR  | Correlation (r):<br>0.39 SO <sub>2</sub>   |
| † <a href="#">Kim et al. (2015)<sup>c</sup></a><br>Seoul, South Korea<br>2008–2011<br>All ages      | Number of monitors not<br>reported             | 24.8                                     | 75th: 30.8  | Correlation (r):<br>0.02 O <sub>3</sub> , 0.6<br>PM <sub>10–2.5</sub><br>Copollutant<br>models with: NA  |

**Table 5-1 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range  | Exposure Assessment | Mean Concentration<br>µg/m <sup>3a</sup>                                  | Upper Percentile<br>Concentrations µg/m <sup>3a</sup> | Copollutant<br>Examination   |
|--|---------------------|---|---|--|
| <b>Physician visits</b>  |                     |   |   |  |
| †Sinclair et al. (2010)<br>Atlanta, GA<br>1998–2002<br>All ages                    | One monitor         | Overall: 17.1<br>Aug 1998–Aug 2000:<br>18.4<br>Sep 2000–Dec 2002:<br>16.2 | NR  | Correlation (r):<br>Warm<br>season = 0.63 O <sub>3</sub><br>Copollutant<br>models with: NA |
| <b>Hospital admissions and ED visits, separately</b>                               |                     |   |   |  |
| Slaughter et al. (2005)<br>Spokane, WA<br>1995–1999<br>All ages                    | One monitor         | NR  | 90: 20.2  | Correlation (r):<br>0.62 CO<br>Copollutant<br>models with: NA                              |
| †Winqvist et al. (2012)<br>St. Louis, MO<br>2001–2007<br>All ages, 2–18 yr, ≥65 yr | One monitor         | 14.4  | Max: 56.6   | Correlation (r):<br>0.25 O <sub>3</sub><br>Copollutant<br>models with: NA                  |

**Table 5-1 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions, emergency department (ED) visits, physician visits for asthma.**

| Study, Location, Years, Age Range                        | Exposure Assessment      | Mean Concentration<br>µg/m <sup>3a</sup> | Upper Percentile<br>Concentrations µg/m <sup>3a</sup> | Copollutant<br>Examination   |
|--|--------------------------|--|---|--|
| <b>Hospital admissions and ED visits, combined</b>       |                          |  |   |  |
| †Li et al. (2011)<br>Detroit, MI<br>2004–2006<br>2–18 yr | Average of four monitors | 15.0                                     | 75th: 18.5<br>Max: 69.0                               | Correlation ( <i>r</i> ):<br>Across<br>monitors = 0.59,<br>0.64 NO <sub>2</sub> , 0.53,<br>0.43 SO <sub>2</sub> , 0.30,<br>0.41 CO<br><br>Copollutant<br>models with: NA |

Avg = average, CMAQ = community multiscale air quality model, CO = carbon monoxide, ED = emergency department, max = maximum, NA = not available;  
NO<sub>2</sub> = nitrogen dioxide, NO<sub>x</sub> = sum of NO<sub>2</sub> and nitric oxide, NR = not reported, O<sub>3</sub> = ozone, SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>All data are for 24-hour average unless otherwise specified

<sup>b</sup>Median concentration.

<sup>c</sup>PM<sub>2.5</sub> data only available for 1 year (2010).

†Studies published since the 2009 PM ISA.

#### 5.1.2.1.1 Hospital Admissions

Across recent studies, evidence supports an association between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions, particularly in analyses of children and people of all ages (Figure 5-2). This evidence is supported by studies that examined associations with PM<sub>2.5</sub> within a state, across multiple cities, or individual cities. In 12 California counties encompassing the south coast and central valley, Yap et al. (2013) focused on examining the influence of socioeconomic status (SES) on hospital admissions for pediatric (children ages 1 to 9 years) respiratory conditions associated with PM<sub>2.5</sub> exposure (CHAPTER 12). For childhood asthma hospital admissions, the authors reported positive associations across each individual city with varying width of confidence intervals, resulting in relative risks for south coast and central valley combined ranging from 1.03–1.07 at lag 0–2 days. While Yap et al. (2013) reported evidence of positive associations in children, Bell et al. (2015) in a study of 213 U.S. counties focusing on older adults (i.e., ≥65 years of age), 70 of which had asthma data, did not observe an increase in asthma hospital admissions (RR = 1.00 [95% CI: 0.99, 1.01]; lag 1), but the authors only examined single-day lags.

Additional single-city studies conducted in the U.S., Canada, and internationally further examined associations between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions in different age groups (i.e., people of all ages, children, and older adults). In New York City, Silverman and Ito (2010) focused on asthma hospital admissions consisting of severe episodes that required a stay in the intensive care unit (ICU) and those that did not (non-ICU) across several different age ranges. Due to the focus on both PM<sub>2.5</sub> and O<sub>3</sub>, the study authors limited analyses to the warm season (April–August). The authors examined people of all ages as well as children and adults. An increased risk for total asthma hospital admissions (combined ICU and non-ICU) for children 6–18 years of age was reported for PM<sub>2.5</sub> (RR = 1.16 [95% CI: 1.10, 1.22]; lag 0–1). An elevated risk due to PM<sub>2.5</sub> exposure was also evident when examining both ICU and non-ICU admissions for children 6–18 years of age (Figure 5-2). Results similar in magnitude were observed for both children and people of all ages, with associations smaller in magnitude and with wider confidence intervals for ages 50 and older. The results of Silverman and Ito (2010) are consistent with a study conducted by Winquist et al. (2012) in St. Louis, MO that also examined associations across several age ranges. Winquist et al. (2012), reported the strongest evidence of an association when examining people of all ages and children 2–18 years of age, with no evidence of an association for older adults (Figure 5-2). Kim et al. (2012) in a study in Denver, CO examined a longer lag structure, a 14-day distributed lag model, and reported evidence of a positive association between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions for people of all ages (quantitative results not presented). However, Liu et al. (2016) in a study conducted in the greater Houston area, did not report evidence of an association with PM<sub>2.5</sub> and unscheduled hospital admissions (quantitative results not presented). It is important to note that the population examined in Liu et al. (2016) consisted of individuals with private insurance, which differs from the other studies evaluated in this section that did

not differentiate amongst insurance coverage when identifying hospital admissions; therefore, the results may not be comparable.

Studies that examined several age ranges tended to indicate stronger associations, in both magnitude and precision, for children. Additional studies focusing only on children provide supporting evidence for associations between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions. [Li et al. \(2011\)](#) in Detroit, MI; [Chen et al. \(2016\)](#) in Adelaide, Australia; and [Iskandar et al. \(2012\)](#) in Copenhagen, Denmark all reported evidence of positive associations at lag 0–4 days ([Figure 5-2](#)).

#### 5.1.2.1.2 Emergency Department (ED) Visits

Similar to hospital admission studies, recent ED visit studies provide evidence of generally consistent positive associations with short-term PM<sub>2.5</sub> exposures, particularly when examining children and people of all ages ([Figure 5-3](#)). However, compared to the hospital admission studies, the magnitude of the association tends to be smaller for ED visits. The evidence supporting an association between short-term PM<sub>2.5</sub> exposure and asthma ED visits is derived from studies conducted over an entire state, across multiple cities, or in individual cities. Additional studies focusing on exposure-related issues, such as exposure assignment ([Sarnat et al., 2013b](#); [Strickland et al., 2011](#)) and air exchange rates ([Sarnat et al., 2013a](#)), have also focused on examining the relationship between short-term PM<sub>2.5</sub> exposure and asthma ED visits. They provide additional supporting evidence, but are characterized in [CHAPTER 3](#) (Section [3.3.2.1](#) and Section [3.3.2.4.2](#)).

Both [Malig et al. \(2013\)](#) and [Ostro et al. \(2016\)](#) in multilocation studies conducted in California that focused on people of all ages, 35 counties and 8 metropolitan areas, respectively, provided evidence of positive associations at lag 0. [Ostro et al. \(2016\)](#) reported an OR = 1.01 (95% CI: 1.00, 1.02), and [Malig et al. \(2013\)](#) reported an OR = 1.02 (95% CI: 1.01, 1.03). These results are consistent with [Weichenthal et al. \(2016\)](#) in a study that encompassed Ontario, Canada that also reported a positive association with asthma ED visits for people of all ages but encompassed a multiday lag of 0–2 days. [Krall et al. \(2016\)](#) in a study of four U.S. cities (i.e., Atlanta, GA; Birmingham, AL; St. Louis, MO; and Dallas, TX) that primarily focused on PM<sub>2.5</sub> sources also reported positive associations with asthma/wheeze ED visits in city-specific analyses for people of all ages at lag 3 (quantitative results not presented). Additional evidence from single-city studies conducted in St. Louis, MO ([Sarnat et al., 2015](#); [Winquist et al., 2012](#)) and Seoul, South Korea ([Kim et al., 2015](#)) report associations similar in magnitude to the multilocation studies, but with wider confidence intervals ([Figure 5-3](#)). However, [Byers et al. \(2015\)](#) did not report evidence of an association for asthma hospital admissions for people of all ages in a study conducted in Indianapolis, IN (RR = 0.99 [95% CI: 0.98, 1.01]; lag 0–2).

While a few of the studies that conducted analyses focusing on people of all ages also include analyses focusing on other age ranges including children ([Byers et al., 2015](#); [Winquist et al., 2012](#)), several recent studies focus exclusively on the relationship between short-term PM<sub>2.5</sub> exposure and

1 asthma ED visits in children. Both [Winqvist et al. \(2012\)](#) and [Byers et al. \(2015\)](#) reported associations  
2 larger in magnitude in children compared to people of all ages combined in St. Louis, MO (RR = 1.05  
3 [95% CI: 1.02, 1.09]; lag 0–4) and Indianapolis, IN (RR = 1.01 [95% CI: 0.98, 1.05]; lag 0–2),  
4 respectively. The results of [Winqvist et al. \(2012\)](#) and [Byers et al. \(2015\)](#) are consistent with single-city  
5 ([Strickland et al., 2010](#)) and whole state ([Xiao et al., 2016](#); [Gleason and Fagliano, 2015](#); [Strickland et al.,](#)  
6 [2015](#)) analyses that focused on pediatric asthma ED visits ([Figure 5-3](#)), with ORs and RRs across studies  
7 ranging from 1.01–1.05. An additional multicity study encompassing three U.S. cities (i.e., Atlanta, GA,  
8 St. Louis, MO; and Dallas, TX), which also examined associations in older adults, provides additional  
9 support for the associations observed in other recent studies focusing on children (RR = 1.03 [95% CI:  
10 1.01, 1.05]; lag 0–2) ([Alhanti et al., 2016](#)).

11 Most of studies that examined the association between short-term PM<sub>2.5</sub> exposure and asthma ED  
12 visits focused on analyses for people of all ages and/or children, with a more limited number of studies  
13 examining potential PM<sub>2.5</sub> effects in adults and older adults ([Alhanti et al., 2016](#); [Byers et al., 2015](#);  
14 [Winqvist et al., 2012](#)). Both [Byers et al. \(2015\)](#) in Indianapolis, IN and [Winqvist et al. \(2012\)](#) in St. Louis,  
15 MO reported evidence of a null association with asthma ED visits in adults 45 and older, and 65 and  
16 older, respectively ([Figure 5-3](#)). However, [Alhanti et al. \(2016\)](#) in three U.S. cities reported a RR = 1.03  
17 (95% CI: 0.99, 1.06) at lag 0–2. Although [Alhanti et al. \(2016\)](#) included St. Louis, MO in the three U.S.  
18 cities examined, when examining city-specific results, the overall association is heavily influenced by  
19 Atlanta, GA with the St. Louis, MO result being consistent with that reported in [Winqvist et al. \(2012\)](#).

#### 5.1.2.1.3 Summary of Asthma Hospital Admissions and Emergency Department (ED) Visits

20 Building off the evidence detailed in the 2009 PM ISA ([U.S. EPA, 2009](#)), recent epidemiologic  
21 studies strengthen the evidence for a relationship between short-term PM<sub>2.5</sub> exposure and asthma-related  
22 hospital admissions and between short-term PM<sub>2.5</sub> exposure and ED visits in analyses of children and  
23 people of all ages. Evidence for a relationship in older adults continues to be inconsistent. The main  
24 results of studies detailed within this section are supported by analyses that examined specific  
25 policy-relevant issues as detailed in [Section 5.1.10](#). Specifically, analyses of potential copollutant  
26 confounding provide evidence that PM<sub>2.5</sub> associations are relatively unchanged in models with gaseous  
27 pollutants and PM<sub>10–2.5</sub>, but the evidence is more limited for PM<sub>10–2.5</sub> ([Section 5.1.10](#)). Although in some  
28 instances the results from copollutant models are attenuated, they remain positive overall. The  
29 associations observed across studies were found to be robust in sensitivity analyses that examined  
30 alternative model specifications to account for temporal trends as well as the potential confounding  
31 effects of weather.

32 Additionally, the overall body of evidence indicating a relationship between short-term PM<sub>2.5</sub>  
33 exposure and asthma hospital admissions and ED visits is supported by studies that conducted analyses to  
34 further elucidate this relationship. Across studies that examined whether there was evidence of seasonal

patterns, studies that divided the year into warm and cold season reported associations larger in magnitude for the warmer months. These results are supported by studies that examined all four seasons of the year, but they also indicate that effects may be strongest over more defined periods of the year (i.e., the spring) (Section 5.1.10.4.1). Additionally, examinations of the concentration-response (C-R) relationship provide some evidence for a log-linear relationship for short-term PM<sub>2.5</sub> exposure and asthma hospital admissions and ED visits. However, complicating the interpretation of these results is both the lack of thorough empirical evaluations of alternatives to linearity as well as the results from cutpoint analyses that provide some potential indication for nonlinearity in the relationship between short-term PM<sub>2.5</sub> exposure and asthma hospital admission and ED visits (Section 5.1.10.6).

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### 5.1.2.2 Respiratory Symptoms and Asthma Medication Use in Populations with Asthma

Studies evaluating the effects of short-term PM<sub>2.5</sub> exposure on respiratory symptoms and asthma medication use consisted solely of epidemiologic studies. Results will be discussed separately for children with asthma and for adults with asthma.

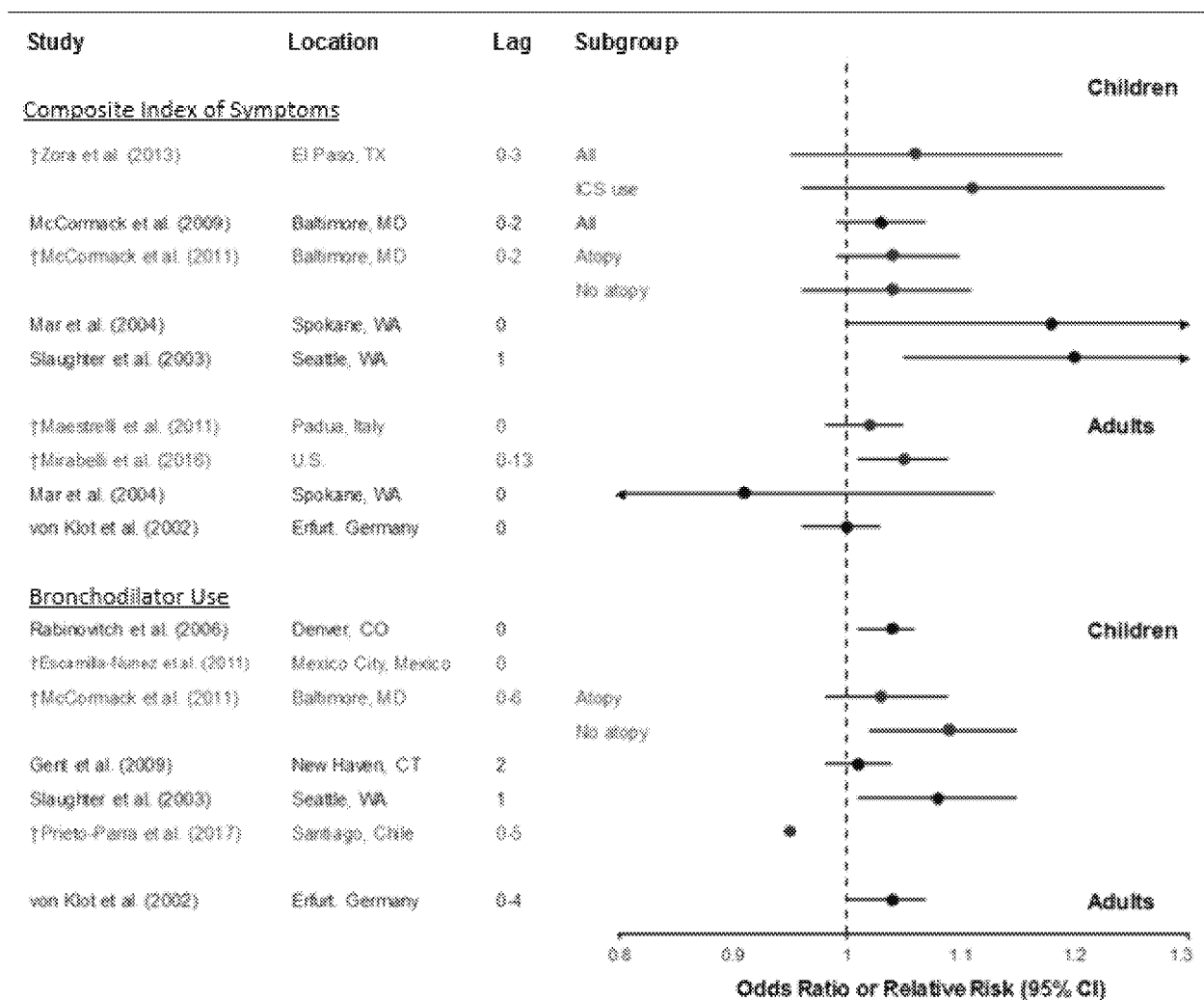
#### Children

Uncontrollable respiratory symptoms, such as cough, wheeze, sputum production, shortness of breath, and chest tightness, can lead people with asthma to seek medical care. Thus, along with medication use in children, studies examining the relation between PM<sub>2.5</sub> and increases in asthma symptoms may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.1.2.1. A limited number of panel studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provide evidence of an association between PM<sub>2.5</sub> and respiratory symptoms (Mar et al., 2004; Gent et al., 2003; Slaughter et al., 2003) and medication use (Gent et al., 2009; Rabinovitch et al., 2006; Slaughter et al., 2003) in children with asthma. In studies that examined copollutant confounding, associations between PM<sub>2.5</sub> and asthma severity were robust to the inclusion of CO in a copollutant model (Slaughter et al., 2003), while PM<sub>2.5</sub> associations with persistent cough, chest tightness, and shortness of breath no longer persisted in models adjusting for O<sub>3</sub> (Gent et al., 2003).

A few recent studies provide some additional evidence of an association between PM<sub>2.5</sub> and a composite index of multiple symptoms (Figure 5-4). In a panel study including 90 schoolchildren with asthma in Santiago, Chile, PM<sub>2.5</sub> concentrations were associated with increases in coughing and wheezing, as well as a composite index of respiratory symptoms (Prieto-Parra et al., 2017). The observed associations were strongest in magnitude for 7-day average PM<sub>2.5</sub>. Similarly, among children at two schools in El Paso, TX, 5-day average PM<sub>2.5</sub> concentrations measured outside of the schools were associated with poorer asthma control scores, which reflect symptoms and activity levels (Zora et al., 2013). The two schools included in the study differed in nearby traffic levels but varied similarly in

1 outdoor PM<sub>2.5</sub> concentration over time (Section 3.4.3.1). In contrast, students attending schools with  
2 varying nearby traffic levels were also examined in the Bronx, NY, though asthma symptoms were not  
3 associated with outdoor school or total personal PM<sub>2.5</sub> concentrations (Spira-Cohen et al., 2011). A low  
4 correlation between school and personal PM<sub>2.5</sub> concentrations ( $r = 0.17$ ) and a reportedly high proportion  
5 of time spent indoors (89%), suggests that personal PM<sub>2.5</sub> exposure was largely influenced by indoor  
6 rather than ambient sources. In an additional study related to respiratory symptoms, asthma-related school  
7 absence was associated with 19-day average PM<sub>2.5</sub> concentrations in a U.S. multicity study (O'Connor et  
8 al., 2008). Notably, confounding by meteorological factors is difficult to control with long averaging  
9 times. Study-specific details, including cohort descriptions and air quality characteristics are highlighted  
10 in Table 5-2.

11 In addition to respiratory symptoms, recent studies of medication use in children add to the  
12 limited evidence base, providing some additional evidence of PM<sub>2.5</sub>-associated increases in the use of  
13 bronchodilators, which can provide quick relief from asthma symptoms (Figure 5-4). Panel studies of  
14 schoolchildren with asthma in Denver, CO (Rabinovitch et al., 2011) and Mexico City (Escamilla-Núñez  
15 et al., 2008) observed associations between PM<sub>2.5</sub> concentrations and bronchodilator use. Escamilla-  
16 Núñez et al. (2008) reported comparable associations using lag 0 and 5-day average PM<sub>2.5</sub>, while  
17 Rabinovitch et al. (2011) observed associations that were stronger in magnitude when estimated using  
18 2-day moving average PM<sub>2.5</sub> compared to single-day lags. In contrast, PM<sub>2.5</sub> concentrations were  
19 associated with decreased bronchodilator use in a panel study in Santiago, Chile (Prieto-Parra et al.,  
20 2017).



Note: †Studies published since the 2009 PM ISA. Studies in black were included in the 2009 PM ISA. Effect estimates are standardized to a 10  $\mu\text{g}/\text{m}^3$  increase in 24-hour average  $\text{PM}_{2.5}$ . CI = confidence interval, ICS = inhaled corticosteroid. Lag times reported in days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-4 Summary of associations between short-term  $\text{PM}_{2.5}$  exposures and respiratory symptoms and medication use in populations with asthma.**

**Table 5-2 Epidemiologic studies of PM<sub>2.5</sub> and respiratory symptoms and medication use in children with asthma.**

| Study  | Study Population  | Exposure Assessment   | Concentration (µg/m <sup>3</sup> )  | PM <sub>2.5</sub> Copollutant Model Results and Correlations  |
|--|---|---|---|---|
| † <a href="#">Spira-Cohen et al. (2011)</a><br>Bronx, NY<br>2002–2005  | N = 40, ages 10–12 yr<br>78% with rescue inhaler use<br>Daily diary for 1 mo<br>No information on participation rate<br>89% time spent indoors                | School outdoor and total personal<br>24-h avg<br>$r = 0.17$ school and personal<br>children walk to school  | Mean<br>School: 14.3<br>Total personal: 24.1  | Correlation ( $r$ ): NA<br>Copollutant models with: NA  |
| † <a href="#">Zora et al. (2013)</a><br>El Paso, TX<br>Mar–Jun 2010  | N = 36, ages 6–11 yr<br>33% ICS use, 47% atopy<br>Weekly measures for 13 weeks<br>95% follow-up participation   | School outdoor<br>96-h avg<br>Two schools: High and low traffic area<br>$r = 0.89$ between schools, 0.91<br>between monitors, 0.73–0.86<br>school and monitor | Mean, max<br>School 1: 13.8, 24.9<br>School 2: 9.9, 18.5  | Correlation ( $r$ ): (School 1,<br>School 2) –0.33, –0.19 NO <sub>2</sub> ;<br>–0.02, 0.25 benzene; 0.10,<br>0.33 toluene; 0.47, 0.28 O <sub>3</sub><br>Copollutant models with: NA |
| † <a href="#">Rabinovitch et al. (2011)</a> ; <a href="#">Rabinovitch et al. (2006)</a><br>Denver, CO<br>2002–2005 | N = 82 (3-yr study), 73 (2-yr study)<br>65–86% moderate/severe asthma,<br>82–90% ICS use<br>Daily measures for 4–7 mo<br>No information on participation rate | One monitor<br>24-h avg, 10-h avg (12–11 a.m.),<br>1-h max (12–11 a.m.)<br>4.3 km from school<br>$r = 0.92$ monitor and school                                | Mean, max for yr 1–3<br>24-h avg: 6.5–8.2, 20.5–23.7<br>10-h avg: 7.4–9.1, 22.7–30.2<br>1-h max: 16.8–22.9, 39–52<br>(95th) | Correlation ( $r$ ): NA<br>Copollutant models with: NA  |
| † <a href="#">Escamilla-Núñez et al. (2008)</a><br>Mexico City, Mexico<br>2003–2005                                | N = 147, ages 9–14 yr<br>43% persistent asthma, 89% atopy<br>Daily diary for mean 22 weeks<br>94% follow-up participation                                     | One monitor<br>24-h avg<br>Within 5 km of school or home<br>$r = 0.77$ monitor and school   | Mean: 27.8  | Correlation ( $r$ ): 0.62 NO <sub>2</sub> ,<br>0.54 O <sub>3</sub><br>Copollutant models with: NA   |

**Table 5-2 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory symptoms and medication use in children with asthma.**

| Study   | Study Population   | Exposure Assessment  | Concentration (µg/m <sup>3</sup> )             | PM <sub>2.5</sub> Copollutant Model Results and Correlations  |
|---|--|--|--|---|
| <u>Prieto-Parra et al. (2017)</u><br>Santiago, Chile<br>May–Sep 2010–2011 | N = 89, ages 6–14 yr<br>50% mild asthma, 53% ICS use, 64% atopy<br>Daily diary for 3 mo<br>79% follow-up participation   | One monitor<br>Most homes within 3 km                                      | Mean: 30                                       | Correlation ( <i>r</i> ): NA<br>Copollutant models with: PM <sub>10</sub> , NO <sub>2</sub> , O <sub>3</sub> , SO <sub>2</sub> , K, Mo, Pb, S, Se, and V      |
| <u>†Mann et al. (2010)</u><br>Fresno, Clovis, CA<br>2000–2005             | N = 280, mean (SD) age 8.1 (1.7)<br>25% moderate/severe asthma, 38% ICS use, 63% atopy<br>Daily diary for 2 weeks, every 3 mo<br>89% participation from enrolled | One monitor<br>24-h avg<br>Within 20 km of home                            | Median: 18.7<br>75th: 32.0<br>Max: 137         | Correlation ( <i>r</i> ): 0.63 NO <sub>2</sub> , –0.45 O <sub>3</sub> , –0.23 PM <sub>10–2.5</sub> , 0.76 EC<br>Copollutant models with: PM <sub>10–2.5</sub> |
| <u>Gent et al. (2009)</u><br>New Haven, CT<br>2000–2004                   | N = 149, ages 4–12 yr<br>33% moderate/severe asthma<br>Daily diary for mean 313 days<br>No information on participation  | One monitor<br>24-h avg<br>Near highway, 0.9–27 km from homes (mean 10 km) | Mean: 17.0                                     | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA   |
| <u>Slaughter et al. (2003)</u><br>Seattle, WA<br>Years NR                 | N = 133, ages 5–12 yr<br>100% mild/moderate asthma<br>Daily diary for 28–112 days<br>No information on participation   | Three monitors averaged<br>24-h avg  | NR   | Correlation ( <i>r</i> ): 0.82 CO<br>Copollutant models with: CO  |
| <u>Mar et al. (2004)</u><br>Spokane, WA<br>1997–1999                      | N = 9, ages 7–12 yr<br>100% regular medication use<br>Daily diary for mean 580 days<br>No information on participation   | One monitor  | Means<br>1997: 11.0<br>1998: 10.3<br>1999: 8.1 | Correlation ( <i>r</i> ): 0.61 PM <sub>10</sub> , 0.92 PM <sub>1</sub> , 0.28 PM <sub>10–2.5</sub><br>Copollutant models with: NA                             |

Avg = average, CO = carbon monoxide, ICS = inhaled corticosteroid use, IQR = interquartile range, max = maximum, NO<sub>2</sub> = nitrogen dioxide, NR = not reported, O<sub>3</sub> = ozone, PM<sub>2.5</sub> = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; RR = relative risk, SD = standard deviation, SO<sub>2</sub> = sulfur dioxide.

†Studies published since the 2009 PM ISA.

Recent evidence of associations from studies that measured PM<sub>2.5</sub> concentrations outside of children's schools, representing exposure where children spend a large part of their day, increases confidence in the associations observed. Additionally, recruitment mostly occurred at schools; thus, the study populations were likely representative of the general population of children with asthma. The representativeness of results is also supported by the high follow-up participation rates (79–95%; Table 5-2). Meanwhile, potential copollutant confounding remains a source of uncertainty given the lack of studies that report copollutant models. In limited copollutant results described in the 2009 PM ISA (U.S. EPA, 2009), PM<sub>2.5</sub> associations appeared robust to adjustments for CO, but not O<sub>3</sub>, despite high copollutant correlation ( $r > 0.7$ ) (Gent et al., 2003; Slaughter et al., 2003). Recent studies show moderate correlations ( $0.4 < r < 0.7$ ) for PM<sub>2.5</sub> with O<sub>3</sub> and NO<sub>2</sub> (Table 5-2), though only a single study presented copollutant models. The association between PM<sub>2.5</sub> and asthma control in schoolchildren was attenuated but still positive with adjustment for NO<sub>2</sub>, O<sub>3</sub>, benzene, or toluene, which were all weakly to moderately correlated ( $r < 0.5$ ) with PM<sub>2.5</sub> (Zora et al., 2013). Further discussion of copollutant confounding is provided in Section 5.1.10.1.

## Adults

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) reported inconsistent evidence of an association between PM<sub>2.5</sub> and respiratory symptoms and medication use in adults with asthma. Recent studies provide limited evidence of association between PM<sub>2.5</sub> and respiratory symptoms or markers for medication use in adults with asthma (Figure 5-4). A U.S.-wide cross-sectional analysis indicates increases in any asthma symptom with increases in county-average PM<sub>2.5</sub> concentrations modeled by CMAQ (Mirabelli et al., 2016). Analysis of the concentration-response relationship isolates the association to lower concentrations, ranging from 4.0 to 7.1 µg/m<sup>3</sup>. However, this study is limited by its cross-sectional design, and residual confounding may arise from the 14-day PM<sub>2.5</sub> averaging time and lack of consideration of confounding by community-level SES. A recent study in Milan, Italy measured levels of the beta-agonist salbutamol in untreated wastewater samples to estimate the daily population-level use of short-acting beta-antagonists (Fattore et al., 2016). Single-day PM<sub>2.5</sub> lags, ranging from 0 to 10 days, were associated with increases in daily defined doses of short-acting beta-antagonists, with associations that were strongest in magnitude at lags 7 and 8 (RR = 1.07 [95% CI: 1.02, 1.12]). The validity and reliability of wastewater levels of medication as an indicator for medication use is untested, but previous results show increases in self-reported beta-agonist and ICS use with increases in PM<sub>2.5</sub> concentrations averaged over 5 days (von Klot et al., 2002). Other recent studies of associations between personal exposure to PM<sub>2.5</sub> and respiratory symptoms, examined in aggregate or individually, are limited by simple correlation analyses on observations (Larsson et al., 2010) or by temporal mismatch between 2-day PM<sub>2.5</sub> exposure and 4-week symptom interval (Maestrelli et al., 2011).

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### 5.1.2.3 Lung Function Changes in Populations with Asthma

Studies evaluating the effects of short-term PM<sub>2.5</sub> exposure on lung function consisted solely of epidemiologic studies. Results will be discussed separately for children with asthma and for adults with asthma. Some studies in adults employed scripted exposures to further inform the relationship between short-term PM<sub>2.5</sub> exposure and lung function. Scripted studies measuring personal ambient PM<sub>2.5</sub> exposures are designed to minimize uncertainty in the PM<sub>2.5</sub> exposure metric by always measuring PM<sub>2.5</sub> at the site of exposure, ensuring exposure to sources of PM<sub>2.5</sub> and measuring outcomes at well-defined lags after exposure.

#### Children

Lung function metrics can indicate airway obstruction, which is the defining characteristic of asthma. Further, specific lung function metrics, such as FEV<sub>1</sub>, have been shown to have prognostic value for asthma exacerbation (Pijnenburg et al., 2015), such that PM<sub>2.5</sub>-related decrements in lung function may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.1.2.1. In the 2009 PM ISA (U.S. EPA, 2009), several panel studies of children with asthma provide generally consistent evidence of an association between short-term PM<sub>2.5</sub> concentrations and decreased FEV<sub>1</sub>. PM<sub>2.5</sub> exposure in particular microenvironments was also associated with lung function decrements in studies examined in the 2009 PM ISA. In Seattle, decrements in some measures of lung function (PEF, MEF, FEV<sub>1</sub>) were associated with PM<sub>2.5</sub> concentrations (Allen et al., 2008; Trenga et al., 2006). Based on the ratio of personal to ambient sulfur concentrations, total personal PM<sub>2.5</sub> exposure was partitioned into ambient-generated and nonambient-generated fractions. Only the ambient-generated PM<sub>2.5</sub> was associated with lung function decrements (FEV<sub>1</sub>, PEF, MEF) (Allen et al., 2008). PM<sub>2.5</sub> concentrations at fixed-site monitors were associated with larger decrements in FEV<sub>1</sub> among children with asthma in Denver, CO after adjusting for an estimate of the ambient-generated portion based on the ratio of personal to ambient sulfur concentrations (Strand et al., 2006). Notably, there was a lack of studies that examined potential confounding by copollutants, raising uncertainties about the independence of the observed associations.

Several recent studies continue to provide evidence of an association between short-term PM<sub>2.5</sub> exposure and FEV<sub>1</sub> decrements in children with asthma. As in studies of respiratory symptoms in children with asthma (Section 5.1.2.2), lung function studies followed children with asthma in an array of cities in the U.S., Canada, and Asia (Table 5-3) that are similar to the locations of studies that examined asthma hospital admissions and ED visits (Section 5.1.2.1). In Riverside and Whittier, CA, personal PM<sub>2.5</sub> and monitor PM<sub>2.5</sub> concentrations were associated with decreased FEV<sub>1</sub> (Delfino et al., 2008). Associations were strongest in magnitude for personal PM<sub>2.5</sub> exposures, particularly those for 1 and 8-hour max concentrations, suggesting that peak exposures in a certain microenvironment may have increased relevance to lung function. Similarly, among children attending two schools with varying nearby traffic levels in the Bronx, NY, Spira-Cohen et al. (2011) reported decrements in FEV<sub>1</sub> in relation to personal

PM<sub>2.5</sub> concentrations averaged in the 12 hours prior to spirometry. The authors did not observe a similar association with PM<sub>2.5</sub> exposure estimated from monitors outside of the schools. In Windsor, Canada, in another panel of schoolchildren with asthma, Dales et al. (2009) observed associations between 24-hour average PM<sub>2.5</sub> concentrations and nighttime FEV<sub>1</sub> decrements, as well as 12-hour average PM<sub>2.5</sub> and diurnal FEV<sub>1</sub>. PM<sub>2.5</sub> exposure was estimated from a city monitor, though most panel subjects reportedly lived within 10 km downwind of the monitor. In contrast with evidence of a relationship between FEV<sub>1</sub> and short-term exposure to PM<sub>2.5</sub>, Smargiassi et al. (2014) reported that lung function was not associated with personal PM<sub>2.5</sub> in a panel study following 72 children with asthma for 10 consecutive days in Montreal, Canada.

Within studies that compared multiple exposure assignment methods, FEV<sub>1</sub> decrements were larger in relation to PM<sub>2.5</sub> exposure estimated from personal samplers compared to fixed-site monitors (Spira-Cohen et al., 2011; Delfino et al., 2008). This is generally consistent with evidence from the 2009 PM ISA (U.S. EPA, 2009) and potentially indicates reduced exposure measurement error in the personal exposure measures. The errors and uncertainties related to various exposure assignment methods (Section 3.3.5), and the relation between personal and ambient concentrations (Section 3.4.1.3) are discussed in further detail in CHAPTER 3. These results for personal exposure also provide some indication that PM<sub>2.5</sub> exposure in microenvironments may have an independent effect on lung function. However, uncertainties remain regarding the independent effect of PM<sub>2.5</sub> given the limited number of studies that examine potential copollutant confounding and the general limitations of copollutant models. A single recent study examined copollutant models, reporting diurnal and nighttime FEV<sub>1</sub> associations with PM<sub>2.5</sub> that were robust to adjustment for O<sub>3</sub> (Dales et al., 2009). Nighttime FEV<sub>1</sub> associations were also generally unchanged in models including NO<sub>2</sub> or SO<sub>2</sub>, while diurnal FEV<sub>1</sub> decrements were attenuated, but still negative. Notably, the correlation between PM<sub>2.5</sub> and O<sub>3</sub> ( $r = 0.26$ ) was much lower than PM<sub>2.5</sub>-NO<sub>2</sub> ( $r = 0.68$ ) and PM<sub>2.5</sub>-SO<sub>2</sub> ( $r = 0.43$ ) correlations. Further discussion of copollutant confounding is provided in Section 5.1.10.1.

A few recent studies also examine other lung function metrics. In the study of schoolchildren in New York, discussed previously, Spira-Cohen et al. (2011) observed an association between 12-hour average personal PM<sub>2.5</sub> exposure and PEF decrements. As with the examination of FEV<sub>1</sub>, the authors did not observe an association with PM<sub>2.5</sub> at school-site monitors. In a panel study of children receiving long-term in-hospital care in Yotsukaido, Japan, PM<sub>2.5</sub> concentrations averaged over the 24 hours prior to spirometry were associated with both morning and evening PEF decrements (Yamazaki et al., 2011). Given the severity of asthma in this population, the results might not be applicable to the general population with asthma. PEF decrements were also associated with 24-hour average PM<sub>2.5</sub> concentrations in a panel of schoolchildren in Seoul, South Korea (Hong et al., 2010). While the authors examined several single-day lags, ranging from 0 to 4 days, they only observed an association at lag 0. As discussed previously, Smargiassi et al. (2014) reported that personal PM<sub>2.5</sub> exposure was not related to an array of lung function metrics, including FVC and FEF<sub>25-75%</sub>.

1           In summary, recent studies add to the existing evidence linking short-term PM<sub>2.5</sub> exposure to  
2 decrements in FEV<sub>1</sub> in children with asthma. While the previously existing evidence base for  
3 PM<sub>2.5</sub>-related decrements in PEF is less consistent than that for FEV<sub>1</sub>, a few recent studies provide  
4 generally consistent evidence indicating an association. Importantly, uncertainty regarding potential  
5 copollutant confounding remains.

**Table 5-3 Epidemiologic studies of PM<sub>2.5</sub> and lung function in populations with asthma.**

| Study  | Study Population  | Exposure Assessment   | Concentration (µg/m <sup>3</sup> )   | PM <sub>2.5</sub> Copollutant Model Results and Correlations   |
|--|---|---|--|--|
| <b>Children</b>  |   |   |  |  |
| †Spira-Cohen et al. (2011)<br>Bronx, NY<br>2002–2005                       | N = 40, ages 10–12 yr<br>78% rescue inhaler use<br>Daily supervised measures—1 mo<br>No information on participation rate<br>89% time spent indoors                   | School outdoor and total personal<br>12-h avg (9 a.m.–9 p.m.), 24-h avg<br><i>r</i> = 0.17 school and personal<br>Most children walk to school  | Mean<br>School: 14.3<br>Total personal: 24.1   | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA  |
| †Delfino et al. (2008)<br>Riverside, Whittier, CA<br>Jul–Dec 2003 and 2004 | N = 53, ages 9–18 yr<br>100% mild/moderate persistent asthma,<br>62% controlled medication use<br>Daily home measures—10 days<br>No information on participation rate | One monitor and total personal<br>24-h avg, 1-h max, 8-h max<br>Within 16 km of homes in<br>Riverside, 8 km in Whittier.<br><i>r</i> = 0.60 personal-monitor<br>100% above limit of detection | Mean, max<br>Monitor, 24-h avg: 23.3,<br>87.2<br>Total personal<br>24-h avg: 31.2, 180<br>1-h max: 90.1, 604<br>8-h max: 46.2, 241 | Correlation ( <i>r</i> ): (personal,<br>ambient) 0.22, 0.51 EC; 0.26,<br>0.62 OC; 0.38, 0.36 NO <sub>2</sub><br>Copollutant models with: NO <sub>2</sub> |
| †Smargiassi et al. (2014)<br>Montreal, Canada<br>Oct 2009–Apr 2010         | N = 72, ages 8–12 yr<br>43% ICS use, 68% atopic<br>Daily supervised measures—10 days<br>No information on participation rate  | Total personal<br>24-h avg<br>12% below limit of detection  | Mean: 9.6<br>75th: 11.7<br>Max: 100  | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA  |
| †Jacobson et al. (2012)<br>Alta Floresta, Brazil<br>Aug–Dec 2006           | N = 56, ages 8–15 yr<br>5% asthma medication use<br>Daily supervised measures—4 mo<br>90% follow-up participation   | School outdoor<br>24-h avg, 6-h avg (12–5:30 a.m.<br>to 6–11:30 p.m.), 12-h avg<br>(12–11:30 a.m. to 12–11:30<br>p.m.)  |  |  |

**Table 5-3 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and lung function in populations with asthma.**

| Study  | Study Population   | Exposure Assessment   | Concentration (µg/m <sup>3</sup> )   | PM <sub>2.5</sub> Copollutant Model Results and Correlations  |
|--|--|---|--|---|
| Allen et al. (2008);<br>Trenga et al. (2006)<br>Seattle, WA<br>1999–2002                                     | N = 17, ages 6–13 yr<br>Most mild persistent asthma, 65% asthma medication use<br>Daily supervised measures—5–10 days, multiple sessions for some subjects<br>No information on participation rate | Outdoor home, total personal, ambient<br>24-h avg<br>Ambient estimated from personal to ambient sulfur ratio and outdoor home PM <sub>2.5</sub> . | Mean median, 75th<br>Outdoor home: 11.2, 14.7<br>Total personal: 11.3, 16.3<br>Ambient: 6.3, 7.6 | Correlation ( <i>r</i> ): (home monitor, ambient monitor) 0.51, 0.56<br>NO <sub>2</sub> ; 0.70, 0.77 CO<br>Copollutant models with: NA  |
| Barraza-Villarreal et al. (2008)<br>Mexico City, Mexico<br>2003–2005   | N = 158, ages 6–14 yr<br>55% mild intermittent asthma, 6% ICS use, 89% atopy<br>Supervised measures every 15 days–mean 22 weeks<br>No information on participation rate                            | One monitor<br>8-h moving avg<br>Within 5 km of school or home<br><i>r</i> = 0.77 monitor–school  | 8-h avg<br>Mean: 28.9<br>Max: 103  | Correlation ( <i>r</i> ): 0.46 O <sub>3</sub> , 0.61 NO <sub>2</sub><br>Copollutant models with: O <sub>3</sub>   |
| O'Connor et al. (2008)<br>Boston, MA; Bronx, Manhattan, NY; Chicago, IL; Dallas, TX; Tucson, AZ; Seattle, WA | N = 861, ages 5–12 yr<br>100% persistent asthma, 100% atopy, 12% ICS use<br>Daily home measures—2 weeks every 2 mo for 2 yr<br>70% maximum measures obtained                                       | Monitors averaged in city<br>Number NR<br>24-h avg<br>Within median 2.3 km of home  | NR   | Correlation ( <i>r</i> ): 0.59 NO <sub>2</sub> , 0.37 SO <sub>2</sub> , –0.02 O <sub>3</sub> , 0.44 CO<br>Copollutant models with: NA   |
| †Dales et al. (2009)<br>Windsor, Canada<br>Oct–Dec 2005  | N = 182, ages 9–14 yr<br>58% medication use<br>Daily home measures—28 days<br>No information on participation rate<br>Mean 1.6 and 2.2 h/day outdoors  | Two monitors averaged<br>24-h avg, 12-h avg (12–8 a.m., 8 a.m.–8 p.m.)<br>99% within 10 km of monitors  | 24-h avg<br>Mean: 7.8<br>75th: 10.0  | Correlation ( <i>r</i> ): –0.26 O <sub>3</sub> , 0.68 NO <sub>2</sub> , 0.43 SO <sub>2</sub><br>Copollutant models with: NO <sub>2</sub> , SO <sub>2</sub> , and O <sub>3</sub> |
| †Yamazaki et al. (2011)<br>Yotsukaido, Japan<br>Oct–Dec 2000   | N = 17, ages 8–15 yr<br>Children in long-term hospital care<br>100% severe, 100% medication use, 100% atopy<br>Daily supervised measures—2–3 mo<br>No information on participation rate            | One monitor next to hospital<br>24-h avg, 1-h avg   | Mean<br>6–7 a.m.: 24.0<br>12–1 p.m.: 26.9<br>6–7 p.m.: 30.0                                      | Correlation ( <i>r</i> ): (morning, noon, evening, night) –0.44, –0.24, –0.27, –0.40 O <sub>3</sub> ; 0.54, 0.78, 0.62, 0.56<br>Copollutant models with: O <sub>3</sub>         |

**Table 5-3 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and lung function in populations with asthma.**

| Study   | Study Population  | Exposure Assessment   | Concentration (µg/m <sup>3</sup> )  | PM <sub>2.5</sub> Copollutant Model Results and Correlations  |
|---|---|---|---|---|
| †Hong et al. (2010)<br>Seoul, South Korea<br>May–Jun 2007 | N = 18, mean (SD) age 9.3 (0.5) yr<br>No information on asthma severity<br>Daily home measures—1 mo<br>No information on participation rate                 | Monitors in city, number NR<br>24-h avg   | Mean: 36.2  | Correlation (r): NA<br>Copollutant models with: NA  |
| <b>Adults</b>   |   |   |   |   |
| McCreanor et al. (2007)<br>London, U.K.<br>2003–2005      | N = 60, ages 19–55 yr<br>100% mild/moderate asthma, 100% AHR, 84% atopy<br>Supervised measures—high and low traffic<br>No information on participation rate | Personal ambient<br>2-h avg (10:30–12:30 a.m.)<br>Scripted exposure walking on high-traffic road and in park, 3 weeks apart | Median, max<br>High-traffic road: 28.3, 76.1<br>Park: 11.9, 55.9                          | Correlation (r): 0.62 UFP, 0.60 NO <sub>2</sub> , 0.76 C, 0.73 EC<br>Copollutant models with: NO <sub>2</sub> |
| †Mirabelli et al. (2015)<br>Atlanta, GA<br>2009–2011      | N = 18, ages NR.<br>Mean FEV <sub>1</sub> : 100% predicted<br>Supervised measures—pre- and post-commute, two exposures<br>93% completed 2nd commute         | Personal in-vehicle<br>2-h avg (7–9 a.m.)<br>Scripted exposure driving car on highway, median 17/13 weeks apart             | Mean (SD)<br>Asthma control > median: 23.8 (11.7)<br>Asthma control < median: 21.5 (11.1) | Correlation (r): NA<br>Copollutant models with: NA  |
| †Maestrelli et al. (2011)<br>Padua, Italy<br>Years NR     | N = 32, mean (SD) age 40 (7.5) yr<br>56% severe asthma, 91% atopy<br>Supervised measures, six over 2 yr<br>76% with ≥ three measures                        | Total personal<br>24-h avg  | NR  | Correlation (r): NA<br>Copollutant models with: NA  |

AHR = airway hyperresponsiveness, avg = average, BTEX = benzene, toluene, ethylbenzene, xylene, CO = carbon monoxide, FEV<sub>1</sub> = forced expiratory volume in 1 second, ICS = inhaled corticosteroid use, IQR = interquartile range, max = maximum, NO<sub>2</sub> = nitrogen dioxide, NR = not reported, O<sub>3</sub> = ozone, PM<sub>2.5</sub> = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; r = correlation coefficient; RR = relative risk, SD = standard deviation, SO<sub>2</sub> = sulfur dioxide, VOCs = volatile organic compounds.

†Studies published since the 2009 PM ISA.

## Adults

A single study evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined the association between short-term exposure to PM<sub>2.5</sub> and lung function in adults with asthma. In a panel of 60 adults with asthma in London, average PM<sub>2.5</sub> concentrations measured over a 2-hour outdoor walk was associated with decrements in FEV<sub>1</sub> and MMEF<sub>25–75%</sub>, but not FVC (McCreanor et al., 2007). Studies published since the completion of the 2009 PM ISA have been limited in number and results are inconsistent. Mirabelli et al. (2015) studied adults with asthma in Atlanta and reported decreased FEV<sub>1</sub> associated with 2-hour average personal PM<sub>2.5</sub> exposure measured 3 hours prior to spirometry. PM<sub>2.5</sub> concentrations were measured during scripted commutes through rush hour traffic, resulting in higher exposure levels. The observed associations were stronger in magnitude and more precise in participants with poorly controlled asthma. In contrast, in Padua, Italy, Maestrelli et al. (2011) tested the relationship between FEV<sub>1</sub> and 24-hour average personal PM<sub>2.5</sub> exposure the day before spirometry and reported no association in adults with asthma. This study was limited by a design that designated six single-day examination visits across a 2-year period, precluding the opportunity to examine alternative exposure lags. Additionally, low variability in personal PM<sub>2.5</sub> measurements may have contributed to the lack of an observed association.

### 5.1.2.3.1 Controlled Human Exposure Studies

Individuals with pre-existing airway diseases such as asthma, may suffer increased deleterious health effects from exposure to PM compared with individuals without pre-existing airway disease. Increased susceptibility of a PM<sub>2.5</sub>-related health effect may be associated with specific mechanisms known to underlie the pathology of asthma, namely elevated inflammation and altered immune activity. However, there is little evidence from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that exposure to PM<sub>2.5</sub> results in decrements in lung function in individuals with asthma. Although a study evaluated in the 2009 PM ISA Petrovic et al. (2000) observed that a 2-hour exposure to PM<sub>2.5</sub> CAPs (92 µg/m<sup>3</sup>) resulted in decreases in thoracic gas volume in healthy volunteers, other measures of lung function (spirometry, diffusing capacity, airway resistance) were unaffected. This general lack of effect of PM<sub>2.5</sub> exposure on lung function has also been shown in a study investigating the exposure of individuals with asthma to PM<sub>2.5</sub> CAPs (Gong et al., 2003). A recent study examining the respiratory effects of PM<sub>2.5</sub> on individuals with asthma has been conducted by (Urch et al., 2010) using a CAP facility for PM<sub>2.5</sub> located in downtown Toronto, Canada (study details in Table 5-4). Exposure to either PM<sub>2.5</sub> CAPs alone or in addition to O<sub>3</sub> was not observed to affect any measurement of pulmonary function, breathing parameters (tidal volume, breathing frequency, minute ventilation), or airway responsiveness (PC20), compared to filtered air control exposures. The lack of effect of PM<sub>2.5</sub> CAPs on respiratory function observed in Urch et al. (2010) is consistent with the results of previous controlled human exposure studies in which worsening of pulmonary function was not observed.

**Table 5-4 Study-specific details from a controlled human exposure study of short-term PM<sub>2.5</sub> exposure and lung function in individuals with asthma.**

| Study                     | Study Design                    | Disease Status;<br>n; Sex  | Exposure Details<br>(Concentration;<br>Duration; Comparison<br>Group   | Endpoints Measured   |
|---------------------------|---------------------------------|--|--|--|
| <u>Urch et al. (2010)</u> | Blinded randomized block design | Healthy nonsmokers (13) and individuals with asthma (10); n = 23; 11 M, 12 F | PM <sub>2.5</sub> CAPs only: 64 ± 3 or 140 ± 6 µg/m <sup>3</sup> PM <sub>2.5</sub><br>CAPs + O <sub>3</sub> : 68 ± 5 or 142 ± 7 µg/m <sup>3</sup><br>PM <sub>2.5</sub> + 119 ± 1 ppb O <sub>3</sub><br>Comparison group for both groups was filtered air; all exposures were for 2 h carried out at rest | Spirometry (pre-, 10-min, and 20-h post-exposure); Flow-volume, DLCO, MV, VT |

CAPs = concentrated ambient particles; DLCO = diffusion capacity for CO; MV = minute volume; VT = tidal volume.

#### 5.1.2.3.2 Animal Toxicological Studies

The 2009 ISA for PM (U.S. EPA, 2009) evaluated a limited number of inhalation studies examining pulmonary function in animal models of allergic airway disease, which share phenotypic features with asthma in humans. One study reported increased airway responsiveness to methacholine, as indicated by Penh, following short-term exposure to DE. However, this study did not distinguish between effects due to particles and gases in the mixture. No additional studies have become available since that time. In many animal studies, changes in ventilatory patterns are assessed using whole-body plethysmography, for which measurements are reported as Penh. Some investigators consider Penh solely an indicator of altered ventilatory timing (see [Section 5.1.7.4](#)) in the absence of other measurements to confirm changes in airway responsiveness.

#### 5.1.2.3.3 Summary of Lung Function in Populations with Asthma

Overall, panel studies in children with asthma find generally consistent evidence of associations between short-term PM<sub>2.5</sub> exposure and lung function decrements. However, uncertainty regarding potential copollutant confounding remains. Evidence is more limited and less consistent in panel studies involving adults with asthma. Further, several controlled human exposure studies failed to observe lung function decrements in adults with asthma following short-term PM<sub>2.5</sub> exposure. No studies have examined this endpoint in animal models of allergic disease, which share many phenotypic features with asthma in humans.

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#### 5.1.2.4 Subclinical Effects Underlying Asthma Exacerbation

Studies evaluating the effects of short-term PM<sub>2.5</sub> exposure on subclinical effects consisted solely of epidemiologic studies. Results are discussed separately for children with asthma and adults with asthma. Some studies in adults employed scripted exposures to further inform this relationship. Scripted studies measuring personal ambient PM<sub>2.5</sub> exposures are designed to minimize uncertainty in the PM<sub>2.5</sub> exposure metric by always measuring PM<sub>2.5</sub> at the site of exposure, ensuring exposure to sources of PM<sub>2.5</sub> and measuring outcomes at well-defined lags after exposure.

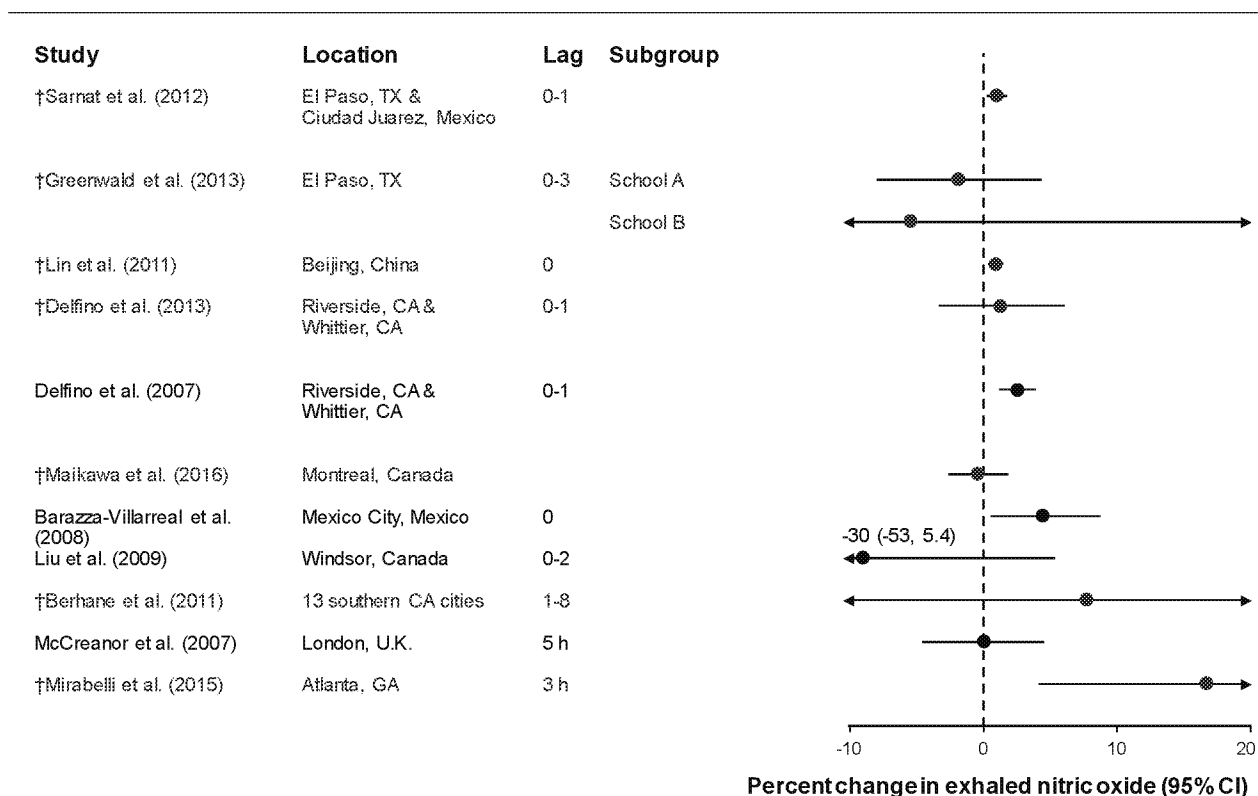
##### Children

Evidence described in the preceding sections for PM<sub>2.5</sub>-related increases in asthma hospital admissions, asthma ED visits, and respiratory symptoms and lung function in children with asthma indicates a potential link between PM<sub>2.5</sub> exposure and asthma exacerbation. The 2009 PM ISA ([U.S. EPA, 2009](#)) also described generally consistent epidemiologic evidence linking increases in pulmonary inflammation in children with asthma to short-term personal PM<sub>2.5</sub> exposure and ambient PM<sub>2.5</sub> concentrations. Most studies examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation. The relevance of eNO to asthma exacerbation is well supported. Levels of eNO have been associated with eosinophil counts ([Brody et al., 2013](#)), which mediate inflammation in allergic asthma. Further, eNO is higher in people with asthma and increases during acute exacerbation ([Soto-Ramos et al., 2013](#); [Kharitonov and Barnes, 2000](#)). In the U.S., associations between short-term PM<sub>2.5</sub> exposure and eNO were observed in panel studies of children with asthma in southern California ([Delfino et al., 2006](#)) and Seattle ([Allen et al., 2008](#); [Koenig et al., 2005](#)). In Seattle, total personal PM<sub>2.5</sub> exposure was partitioned into ambient-generated and nonambient-generated fractions based on the ratio of personal to ambient sulfur concentrations. Only the ambient-generated PM<sub>2.5</sub> was associated with pulmonary inflammation ([Allen et al., 2008](#)). Associations were also observed in most ([Liu et al., 2009](#); [Murata et al., 2007](#); [Fischer et al., 2002](#)), but not all ([Holguin et al., 2007](#)), studies of children outside of the U.S.

Several recent studies provide less consistent evidence of an association between short-term PM<sub>2.5</sub> exposure and pulmonary inflammation in children with asthma ([Figure 5-5](#)). Study-specific details, including cohort descriptions and air quality characteristics are highlighted in [Table 5-5](#). Among children at four schools in the neighboring cities of El Paso, TX and Ciudad Juarez, Mexico, eNO was associated with 48-hour average outdoor PM<sub>2.5</sub> ([Sarnat et al., 2012](#)). Notably, the observed association was largely driven by results from children in one school (Ciudad Juarez) with the highest mean PM<sub>2.5</sub> concentrations. While [Sarnat et al. \(2012\)](#) reported a small, imprecise association between 2-day average outdoor PM<sub>2.5</sub> concentration and eNO in El Paso, a follow-up study of children in the same schools in El Paso observed null associations for 4-day average outdoor PM<sub>2.5</sub> concentrations ([Greenwald et al., 2013](#)). Ambient PM<sub>2.5</sub> concentrations across the two studies were similar ([Table 5-5](#)). A reanalysis of [Delfino et al. \(2006\)](#) confirmed that eNO was not associated with PM<sub>2.5</sub> concentrations measured at fixed-site monitors within 12 km of subjects' residences in a panel study of children with asthma in southern California ([Delfino et](#)

1 al., 2013). However, Delfino et al. (2006) did report an association with personal PM<sub>2.5</sub> in the initial  
2 study. In contrast to evidence of an association between personal PM<sub>2.5</sub> exposure and eNO, Maikawa et al.  
3 (2016) observed a negative association between previous-day personal PM<sub>2.5</sub> exposures and eNO in  
4 62 children with asthma in Montreal, Canada.

5 Other recent studies that used fixed-site monitors to estimate short-term PM<sub>2.5</sub> concentrations  
6 reported more consistent evidence of an association between PM<sub>2.5</sub> and pulmonary inflammation in  
7 children with asthma. Panel studies of children in Beijing, China (Lin et al., 2011) and southern  
8 California (Berhane et al., 2011) reported eNO associations with 24-hour average PM<sub>2.5</sub> concentrations on  
9 the same day of examination and 7-day average concentrations prior to examination, respectively.  
10 Additionally, a panel study of schoolchildren with asthma in Denver, CO (Rabinovitch et al., 2011)  
11 indicated a PM<sub>2.5</sub> association with increases in urinary leukotriene E4, a cytokine involved in  
12 inflammation that is found to increase during asthma exacerbation. Results were similar by asthma  
13 severity, but varied across years, with the PM<sub>2.5</sub>-associated increases in urinary leukotriene E4 limited to 2  
14 of the first 3 study years. Only some children overlapped across years, and PM<sub>2.5</sub> concentrations were  
15 slightly higher in Year 3 (Rabinovitch et al., 2011).



CI = confidence interval.

Note: Studies in red with a dagger are recent studies. Studies in black were included in the 2009 PM ISA. Effect estimates are standardized to a 10  $\mu\text{g}/\text{m}^3$  increase in 24-hour average  $\text{PM}_{2.5}$ . Lag times reported in days. Corresponding quantitative results are reported in Supplemental Material ([U.S. EPA, 2018](#)).

**Figure 5-5 Summary of associations between short-term  $\text{PM}_{2.5}$  exposures and exhaled nitric oxide in populations with asthma.**

**Table 5-5 Epidemiologic studies of PM<sub>2.5</sub> and subclinical effects underlying asthma exacerbation.**

| Study  | Study Population  | Exposure Assessment   | Concentration (µg/m <sup>3</sup> )  | PM <sub>2.5</sub> Copollutant Model Results and Correlations   |
|--|---|---|---|--|
| <b>Children</b>  |   |   |   |  |
| †Sarnat et al. (2012)<br>El Paso, TX; Ciudad Juarez, Mexico<br>Jan–May 2008              | N = 58 (14–15/school), ages 6–12 yr<br>33% ICS use, 41% hay fever<br>Weekly eNO—16 weeks<br>Mean 14 measures/subject, 787 total<br>No information on participation rate | School outdoor<br>48-h avg<br>Schools A and B: Low and high traffic<br>Mean distance home—school: 3.2 km<br><i>r</i> = 0.71–0.93 school-school (within city), 0.91 school-monitor, 0.73–0.86 school-monitor | Mean outdoor<br>Ciudad Juarez A: 31<br>Ciudad Juarez B: 20<br>El Paso A: 8.8<br>El Paso B: 15.6 | Correlation ( <i>r</i> ): (across schools) 0.00, 0.05, –0.39, –0.28 NO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> and NO <sub>2</sub> |
| †Greenwald et al. (2013)<br>El Paso, TX<br>Mar–Jun 2010                                  | N = 38, mean age 10 yr<br>55% ICS use<br>Weekly eNO—13 weeks<br>536 total measures<br>No information on participation rate  | School outdoor<br>96-h avg<br>School A and B: Low and high traffic<br><i>r</i> = 0.89 school-school, 0.91 monitor-monitor, 0.73–0.86 school-monitor (Zora et al., 2013)                                     | Mean (SD) outdoor<br>School A: 9.9<br>School B: 13.8  | Correlation ( <i>r</i> ): 0.20 NO <sub>2</sub> , 0.30 BTEX, 0.44 cleaning product VOCs, 0.37 SO <sub>2</sub><br>Copollutant models with: NA        |
| †Lin et al. (2011); Zhu (2013)<br>Beijing, China<br>Jun, Sep, Dec 2007 and Jun, Sep 2008 | N = 8, ages 9–12 yr<br>Daily eNO—10 days, 5 periods<br>1,581 total measures<br>No information on participation rate   | One monitor, 0.65 km from school<br>24-h avg<br><i>r</i> = 0.56 school-monitor  | Mean across periods<br>212, 96.0, 144, 183, 46.4<br>Max overall: 311                            | Correlation ( <i>r</i> ): 0.30 NO <sub>2</sub><br>Copollutant models with: NO <sub>2</sub> , SO <sub>2</sub> , and CO                              |
| †Delfino et al. (2013)   | N = 45, ages 9–18 yr<br>100% persistent asthma, 64% ICS use<br>Daily eNO—10 days  | One monitor per city<br>24-h avg<br>Within 12 km of Riverside homes, 5 km of Whittier homes   | Mean: 23.2<br>Max: 87.2   | Correlation ( <i>r</i> ): 0.31 NO <sub>2</sub> , 0.39 O <sub>3</sub><br>Copollutant models with: NA  |

**Table 5-5 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and subclinical effects underlying asthma exacerbation.**

| Study   | Study Population   | Exposure Assessment  | Concentration (µg/m <sup>3</sup> )  | PM <sub>2.5</sub> Copollutant Model Results and Correlations  |
|---|--|--|---|---|
| <u>Delfino et al. (2006)</u><br>Riverside, CA<br>Aug–Dec 2003<br>Whittier, CA<br>Jul–Nov 2004 | Number measures NR<br>No information on participation rate   | Total personal, One monitor per city<br>24-h avg, 1-h max<br>$r = 0.91$ monitor-outdoor home.<br>Riverside, $r = 0.77$<br>personal-home, 0.64<br>monitor-personal. | Mean, max<br>Total personal, 24-h avg<br>Riverside: 32.8, 98<br>Whittier: 36.2, 197<br>Total personal, 1-h max<br>Riverside: 37.9, 432<br>Whittier: 93.6, 573<br>Monitor, 24-h avg<br>Riverside: 36.6, 87<br>Whittier: 18, 77 | Correlation ( $r$ ): (personal, monitor) 0.33, 0.25 NO <sub>2</sub><br>Copollutant models with: NO <sub>2</sub> |
| <u>†Maikawa et al. (2016)</u><br>Montreal, Canada<br>Oct 2009–Apr 2010                        | N = 62, ages 8–12 yr<br>15% severe asthma, 24% ICS use, 44% atopy<br>Daily eNO—10 days<br>Median three measures/subject  | Total personal<br>24-h avg<br>60% samples had insufficient mass  | Mean: 19.3<br>Max: 101  | Correlation ( $r$ ): 0.00 O <sub>3</sub><br>Copollutant models with: O <sub>3</sub>                             |
| <u>Allen et al. (2008); Mar et al. (2005)</u><br>Seattle, WA<br>1999–2002                     | N = 17, ages 6–13 yr<br>Most mild persistent asthma, 65% asthma medication use<br>Daily eNO—5–10 days, multiple periods<br>6–20 measures/subject, 226 total<br>No information on participation rate                          | Home outdoor, total personal, ambient<br>24-h avg<br>Ambient estimated from personal to ambient sulfur ratio and outdoor home PM <sub>2.5</sub> .                  | Mean/median, 75th<br>Outdoor home: 11.2, 14.7<br>Total personal: 11.3, 16.3<br>Ambient: 6.3, 7.6  | Correlation ( $r$ ): NA<br>Copollutant models with: NA  |
| <u>†Rabinovitch et al. (2011); Rabinovitch et al. (2006)</u><br>Denver, CO<br>2002–2005       | N = 82 (3-yr study), 73 (2-yr study)<br>65–86% moderate/severe asthma, 82–90% ICS use<br>Daily urinary LTE4—up to 8 days, two periods per yr<br>Median 11–13 measures/subject Yr 1–3<br>No information on participation rate | One monitor<br>24-h avg, 10-h avg (12–11 a.m.), 1-h max (12–11 a.m.)<br>4.3 km from school<br>$r = 0.92$ monitor and school  | Mean, max for Yr 1–3<br>24-h avg: 6.5–8.2, 20.5–23.7<br>10-h avg: 7.4–9.1, 22.7–30.2<br>1-h max: 16.8–22.9, 39–52 (95th)  | Correlation ( $r$ ): NA<br>Copollutant models with: NA  |

**Table 5-5 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and subclinical effects underlying asthma exacerbation.**

| Study   | Study Population   | Exposure Assessment   | Concentration (µg/m <sup>3</sup> )                                     | PM <sub>2.5</sub> Copollutant Model Results and Correlations   |
|---|--|---|--|--|
| <u>Barraza-Villarreal et al. (2008)</u><br>Mexico City, Mexico<br>2003–2005 | N = 158, ages 6–14 yr<br>55% mild intermittent asthma, 6% ICS use, 89% atopy<br>eNO, nasal lavage IL—8 every 15 days—mean 22 weeks<br>702 total measures<br>No information on participation rate | One monitor<br>8-h avg<br>Within 5 km of school or home<br>$r = 0.77$ monitor-school  | Mean: 28.9<br>Max: 103   | Correlation ( $r$ ): 0.46 O <sub>3</sub> , 0.61 NO <sub>2</sub><br>Copollutant models with: O <sub>3</sub>   |
| <u>Liu et al. (2009); Liu (2013)</u><br>Windsor, Canada<br>Oct–Dec 2005     | N = 182, ages 9–14 yr<br>37% ICS use<br>Weekly eNO, TBARS—4 weeks<br>672 total measures<br>No information on participation rate  | Two monitors averaged<br>24-h avg<br>99% homes within 10 km   | Median (IQR): 6.5 (6.0)<br>95th: 19.0                                  | Correlation ( $r$ ): –0.41 O <sub>3</sub> , 0.71 NO <sub>2</sub> , 0.56 SO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> , NO <sub>2</sub> , and SO <sub>2</sub> |
| <u>†Berhane et al. (2011)</u><br>13 southern California cities<br>2004–2005 | N = 169, ages 6–9 yr<br>One eNO measure, cross-sectional<br>No information on participation rate   | One monitor per community<br>24-h avg   | NR   | Correlation ( $r$ ): (warm season, cold season) 0.61, –0.05 O <sub>3</sub> ; 0.47, 0.65 NO <sub>2</sub><br>Copollutant models with: NA                                     |
| <b>Adults</b>   |  |   |  |  |
| <u>McCreanor et al. (2007)</u><br>London, U.K.<br>2003–2005                 | N = 60, ages 19–55 yr<br>100% mild/moderate asthma, 100% AHR, 84% atopy<br>2 eNO measures—high and low traffic<br>No information on participation rate   | Personal ambient<br>2-h avg (10:30–12:30 a.m.)<br>Scripted exposure walking on high-traffic road and in park, 3 weeks apart | Median, max<br>High-traffic road: 28.3, 76.1<br>Park: 11.9, 55.9       | Correlation ( $r$ ): 0.60 NO <sub>2</sub> , 0.76 CO<br>Copollutant models with: NO <sub>2</sub>  |
| <u>†Mirabelli et al. (2015)</u><br>Atlanta, GA<br>2009–2011                 | N = 18, ages NR.<br>Mean FEV <sub>1</sub> : 100% predicted<br>Two measures—pre- and post-commute, Two periods<br>93% completed 2nd commute   | Personal in-vehicle<br>2-h avg (7–9 a.m.)<br>Scripted exposure driving car on highway, median 17/13 weeks apart             | Mean<br>Asthma control > median: 23.8<br>Asthma control < median: 21.5 | Correlation ( $r$ ): NA<br>Copollutant models with: NA   |

**Table 5-5 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and subclinical effects underlying asthma exacerbation.**

| Study   | Study Population   | Exposure Assessment        | Concentration (µg/m <sup>3</sup> ) | PM <sub>2.5</sub> Copollutant Model Results and Correlations |
|---|--|----------------------------|------------------------------------|--|
| †Maestrelli et al. (2011)<br>Padua, Italy<br>Years NR | N = 32, mean (SD) age 40 (7.5) yr<br>56% severe asthma, 69% ICS use, 91% atopy<br>Six eNO measures over 2 yr<br>166 total measures<br>No information on participation rate | Total personal<br>24-h avg | NR                                 | Correlation (r): NA<br>Copollutant models with: NA           |

AHR = airway hyperresponsiveness, avg = average, BTEX = benzene, toluene, ethylbenzene, xylene, CO = carbon monoxide, eNO = exhaled nitric oxide, FEV<sub>1</sub> = forced expiratory volume in 1 second, ICS = inhaled corticosteroid use, IL-8 = interleukin-8, IQR = interquartile range, LTE4 = leukotriene E4, max = maximum, NO<sub>2</sub> = nitrogen dioxide, NR = not reported, O<sub>3</sub> = ozone, PM<sub>2.5</sub> = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; r = correlation coefficient; SD = standard deviation, SO<sub>2</sub> = sulfur dioxide, TBARS = thiobarbituric acid reactive substances, VOCs = volatile organic compounds.

†Studies published since the 2009 PM ISA.

1

1 The inconsistency in recent findings, as related to the 2009 PM ISA, is not explained by lower  
2 PM<sub>2.5</sub> concentrations in recent studies (Table 5-5) but may be influenced by location-specific differences  
3 in PM sources, study populations, or building infiltration characteristics (Section 3.4). Studies evaluated  
4 in the 2009 PM ISA observed associations in locations representing a wide range of PM<sub>2.5</sub> concentrations.  
5 Additionally, a strength of previously reviewed studies of pulmonary inflammation is examination of the  
6 hourly lag structure of PM<sub>2.5</sub> associations. Most (Rabinovitch et al., 2006; Mar et al., 2005) results  
7 indicated an increase in inflammation with increases in PM<sub>2.5</sub> concentrations averaged over the preceding  
8 1 to 11 hours. Associations were also observed with 1-hour or 8-hour max PM<sub>2.5</sub> that were larger in  
9 magnitude than those for 24-hour average PM<sub>2.5</sub> (Delfino et al., 2006; Rabinovitch et al., 2006). Other  
10 results indicate that PM<sub>2.5</sub> exposure may have a rapid and transient effect on pulmonary inflammation in  
11 people with asthma. For Seattle, WA and Riverside and Whittier, CA, distributed lag models show an  
12 increase in eNO with the 1-hour average PM<sub>2.5</sub> concentration up to 5 or 10 hours prior but not with longer  
13 lags of 24–48 hours (Delfino et al., 2006; Mar et al., 2005). This may suggest that some recent studies  
14 have examined exposure windows that were too long to detect an association, though Berhane et al.  
15 (2011) observed eNO associations with cumulative average PM<sub>2.5</sub> up to 30 days.

16 Additionally, recent studies of pulmonary inflammation do not establish an independent  
17 association with PM<sub>2.5</sub> exposure. A recent study presents PM<sub>2.5</sub> associations that are attenuated, but still  
18 positive in copollutant models with NO<sub>2</sub>, SO<sub>2</sub>, or CO (Lin et al., 2011). In a study evaluated in the 2009  
19 PM ISA, personal PM<sub>2.5</sub> associations with eNO were robust to NO<sub>2</sub> adjustment (Delfino et al., 2006). The  
20 result for personal exposure supports an association with PM<sub>2.5</sub> that is independent of NO<sub>2</sub> exposure based  
21 on comparable exposure measurement error and low correlation ( $r = 0.30$ ). However, the limited number  
22 of studies examining additional copollutants, in addition to some inconsistency in the observed  
23 associations in recent studies, leaves uncertainty as to whether PM<sub>2.5</sub> exposure leads to an increase in  
24 pulmonary inflammation in children with asthma. Further discussion of copollutant confounding is  
25 provided in Section 5.1.10.1.

## Adults

26 Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided contrasting evidence of an  
27 association between short-term exposure to PM<sub>2.5</sub> and lung function in adults with asthma. In a panel of  
28 60 adults with asthma in London, average PM<sub>2.5</sub> concentrations measured over a 2-hour outdoor walk was  
29 not associated with eNO measurements taken 3 to 7 hours post-exposure (McCreanor et al., 2007). In  
30 contrast, in a panel of older adults in Seattle, PM<sub>2.5</sub> concentrations measured outside of residences were  
31 associated with eNO in subjects with asthma. Recent studies are limited in number and results are also  
32 inconsistent (Figure 5-5). Mirabelli et al. (2015) studied adults with asthma in Atlanta and reported  
33 increased in eNO associated with 2-hour average personal PM<sub>2.5</sub> exposure measured 0, 1, 2, and 3 hours  
34 prior to spirometry. PM<sub>2.5</sub> concentrations were measured during scripted commutes through rush hour  
35 traffic, resulting in higher exposure levels. The observed associations were stronger in magnitude in

participants with poorly controlled asthma. In contrast, in Padua, Italy, [Maestrelli et al. \(2011\)](#) tested the relationship between eNO and 24-hour average personal PM<sub>2.5</sub> exposure the day before spirometry and reported negative associations in adults with asthma. This study was limited by a design that designated six single-day examination visits across a 2-year period, precluding the opportunity to examine alternative exposure lags.

#### 5.1.2.4.1 Controlled Human Exposure Studies

There were no studies evaluated in the 2009 PM ISA ([U.S. EPA, 2009](#)) that specifically investigated the association between PM<sub>2.5</sub> CAPs exposure and subclinical effects underlying asthma exacerbation. Recently, [Urch et al. \(2010\)](#) investigated the respiratory effects of short-term exposure to PM<sub>2.5</sub> on individuals with asthma by using a CAP facility for PM<sub>2.5</sub> located in downtown Toronto, Canada (study details in [Table 5-6](#)) and found little change in sputum total cell counts, neutrophils, or macrophages when compared to pre-exposure levels.

**Table 5-6 Study-specific details from a controlled human exposure study of short-term PM<sub>2.5</sub> exposure and subclinical effects underlying asthma exacerbation.**

| Study                              | Study Design                    | Disease Status;<br>n; Sex  | Exposure Details<br>(Concentration;<br>Duration; Comparison<br>Group)  | Endpoints Measured   |
|------------------------------------|---------------------------------|--|--|--|
| <a href="#">Urch et al. (2010)</a> | Blinded randomized block design | Healthy nonsmokers (13) and individuals with asthma (10); n = 23; 11 M, 12 F | PM <sub>2.5</sub> CAPs only: 64 ± 3 or 140 ± 6 µg/m <sup>3</sup> PM <sub>2.5</sub><br>CAPs + O <sub>3</sub> : 68 ± 5 or 142 ± 7 µg/m <sup>3</sup><br>PM <sub>2.5</sub> + 119 ± 1 ppb O <sub>3</sub><br>Comparison group for both groups was filtered air; all exposures were for 2 h carried out at rest | Sputum (pre- and 3- and 20-hour post-exposure): IL-6, IL-8, and IL-10, TNF-α, leukotriene-B, differential cell counts<br>Venous blood (pre-, 10-min, and 3- and 20-h post-exposure): IL-6, TNF-α |

CAPs = concentrated ambient particles; IL-6 = Interleukin-6; IL-8 = Interleukin-8; IL-10 = Interleukin-10; O<sub>3</sub> = ozone; TNF-α = tumor necrosis factor α.

#### 5.1.2.4.2 Animal Toxicological Studies

Animal toxicological studies have focused on exacerbation of asthma in the context of allergic airway disease. Allergic airway disease (asthma, rhinitis, etc.) is a type of immune hypersensitivity that is mediated by immunoglobulin E (IgE). Development of allergic airway disease requires sensitization (immunization) that requires, presentation of a foreign antigen by antigen-presenting cells (dendritic cells

1 and macrophage subsets) to T-lymphocytes, the activation and clonal expansion of B-cells, and finally  
2 production of antigen-specific antibody (IgE) that binds to the antigen. Secondary exposure of previously  
3 sensitized individuals to the antigen (challenge, or elicitation phase), will activate IgE-mediated pathways  
4 that result in eosinophil recruitment, mucus production, and reactive airways.

5 The 2009 PM ISA (U.S. EPA, 2009) reviewed the evidence that exposure to PM<sub>2.5</sub> exacerbated  
6 allergic responses in laboratory rodents with pre-existing allergic airway disease. Several studies involved  
7 multiday exposures of ovalbumin (OVA)-sensitized and challenged Brown Norway rats to PM<sub>2.5</sub> CAPs.  
8 Increased nasal and airway mucosubstances, pulmonary inflammation, and retention of anthropogenic  
9 trace elements (La, V, Mn, S) in lung tissue were observed following 4–5 days of exposure to PM<sub>2.5</sub>  
10 CAPs in Detroit, MI (Harkema et al., 2004; Morishita et al., 2004). A 13-day exposure to PM<sub>2.5</sub> CAPs in  
11 Grand Rapids, MI resulted in no changes in BALF cells or gene expression in the whole lung  
12 (Heidenfelder et al., 2009). However, enhanced OVA-specific IgE and Muc5AC responses to ovalbumin  
13 (OVA) were observed. In addition, PM<sub>2.5</sub> CAPs exposure resulted in enhanced allergic bronchiolitis and  
14 alveolitis, as well as in epithelial hypertrophy and mucus cell metaplasia, which are characteristic of  
15 airway epithelial remodeling. Another study showed that enhancement of allergic responses in mice  
16 depended on proximity to the PM source following multiday exposure to roadway PM<sub>2.5</sub> CAPs in Los  
17 Angeles (Kleinman et al., 2005). Additionally, a single acute exposure to reaerosolized diesel exhaust  
18 particles (DEP) resulted in dose-dependent increases in levels of the Th2 cytokine IL-4 in BALF in  
19 allergic mice (Farraj et al., 2006a, b).

20 Recently, Harkema et al. (2009) extended their field studies in Detroit to determine if PM<sub>2.5</sub> CAPs  
21 inhalation would modify the allergic responses during the process of allergen challenge of sensitized rats.  
22 Ovalbumin-sensitized Brown Norway rats that were exposed to Detroit summertime PM<sub>2.5</sub> CAPs for the  
23 same 3 consecutive days of intra-nasal OVA challenge had increased lavaged total protein, secreted  
24 mucosubstances (Muc5AC), and numbers of lymphocytes and eosinophils compared to filtered  
25 air-exposed, allergic rats ( $p < 0.05$ ). PM<sub>2.5</sub> CAPs exposure did not increase OVA-specific IgE levels in  
26 BALF above that seen in response to OVA alone. Decreases in pulmonary gene expression of TNF $\alpha$ ,  
27 IL-10, and IFN $\gamma$  (putative Th1 mediators) were also detected in PM<sub>2.5</sub> CAPs-exposed, OVA-challenged  
28 rats ( $p \leq 0.05$ ). Using the same exposure protocol but in different rats and on different days when PM<sub>2.5</sub>  
29 CAPs concentration was lower; inflammation responses were unaffected by PM<sub>2.5</sub> CAPs exposure. In  
30 addition to having greater PM<sub>2.5</sub> CAPs concentration the first exposure study consisted of PM<sub>2.5</sub> that had  
31 more iron, sulfate, nitrate, and PAH content than during the second exposure study. Additional study  
32 details, for this recent study and a related one, are found in Table 5-7.

**Table 5-7 Study-specific details from animal toxicologic studies of subclinical effects underlying asthma exacerbation.**

| Study/Study Population   | Pollutant  | Exposure   | Endpoints  |
|--|--|--|--|
| <u>Harkema et al. (2009)</u><br>Species: Rat<br>Sex: Male<br>Strain: Brown Norway<br>Age/weight: 10–12 weeks | PM <sub>2.5</sub> CAPs<br>Detroit, MI (urban residential)<br>Particle size: 0.66–0.79 µm<br>Control: Filtered air                                | Route: Whole-body inhalation exposure<br>Dose/concentration: Period 1: 596 µg/m <sup>3</sup><br>Period 2: 356 µg/m <sup>3</sup><br>Duration: 8 h/day, 3 days, two exposure periods in July<br>Time to analysis: 24 h<br>All animals sensitized to OVA.<br>PM <sub>2.5</sub> CAPs inhalation during OVA challenge | Histopathology of nose and lung—light microscopy, airway labelling index<br>BALF cells<br>Gene expression—cytokines and Muc5AC |
| <u>Wagner et al. (2012)</u><br>Species: Rat<br>Strain: Brown Norway<br>Sex: Male<br>Age/weight: 10–12 weeks  | PM <sub>2.5</sub> CAPs<br>Urban Grand Rapids, MI<br>Urban Detroit, MI<br>Particle sizes: PM <sub>2.5</sub><br>Control: HEPA-filtered control air | Route: Whole-body inhalation<br>Dose/concentration (D) Detroit 542 µg/m <sup>3</sup><br>(GR) Grand Rapids 519 µg/m <sup>3</sup><br>Dose/concentration 8 h × 1 day; begun 30 min after intra-nasal OVA challenge<br>Duration of exposure: 8 h<br>Time to analysis: 16 h post exposure                             | PM characterization<br>Histopathology—lung<br>BALF cells<br>Lung injury—BALF protein<br>BALF-Muc5AC content                    |

BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; HEPA = high efficiency particulate absorber; Muc5AC = Mucin 5AC, oligomeric mucus/gel-forming; OVA = ovalbumin.

Morphologic responses to short-term PM<sub>2.5</sub> CAPs exposure was also examined by (Harkema et al., 2009). Both the nose and the lung were evaluated for histologic changes and epithelial cell proliferation. No additional effect on OVA-induced allergic rhinitis was seen in the animals exposed to PM<sub>2.5</sub> CAPs. However, exposure to PM<sub>2.5</sub> CAPs resulted in a greater severity of allergic bronchiolitis and alveolitis in OVA-sensitized and challenged rats. More severe mucus cell metaplasia was found, as evidenced by increased amounts of intra-epithelial mucosubstances in conducting airways ( $p \leq 0.05$ ). Epithelial cell proliferation, as measured by labelling index in the airways, was not altered by PM<sub>2.5</sub> CAPs exposure. When the same exposure protocol was used but in different rats and on different days when PM<sub>2.5</sub> CAPs concentration was considerably lower, morphologic responses were unaffected by PM<sub>2.5</sub> CAPs exposure.

The OVA-allergic Brown Norway rat model was also used to compare the effects of PM<sub>2.5</sub> CAPs exposure that were derived from two dissimilar urban airsheds in Grand Rapids or Detroit MI (Wagner et

al., 2012). Ovalbumin-sensitized rats were challenged with intra-nasal OVA and 30 minutes later breathed similar concentrations of PM<sub>2.5</sub> CAPs for 8 hours. Exposure to Detroit PM<sub>2.5</sub> CAPs, which were characterized by high sulfates and local industrial emissions (high Pb, Zn, and V content), enhanced eosinophilic inflammation ( $p < 0.05$ ), mucus hypersecretion ( $p < 0.05$ ), and mucous cell metaplasia. However, the opposite responses were seen when allergic rats inhaled Grand Rapids PM<sub>2.5</sub> CAPs, which were dominated by a large spike in morning traffic emissions (NO<sub>2</sub>, CO, EC), but had low sulfates throughout the 8-hour exposure. Allergen-induced increases in airway eosinophils ( $p < 0.05$ ), mucus hypersecretion ( $p < 0.05$ ), and mucous cells were reversed in rats exposed to Grand Rapids PM<sub>2.5</sub> CAPs.

In summary, several studies provide evidence that exposure to PM<sub>2.5</sub> CAPs and DEP exacerbates allergic responses. In addition, one study found that PM<sub>2.5</sub> CAPs exposure resulted in an inhibition of allergic responses. These disparate findings may be due to source-related differences in the composition of PM<sub>2.5</sub> CAP due to different locations where the CAPs were collected.

#### 5.1.2.4.3 Summary of Subclinical Effects Underlying Asthma Exacerbation

Overall, panel studies in children with asthma provide some evidence of associations between short-term PM<sub>2.5</sub> exposure and inflammatory markers although uncertainty regarding potential copollutant confounding remains. Results were more consistent with shorter lag times. Evidence is mainly negative in panel studies and controlled human exposure studies involving adults with asthma. Further, several studies found that short-term PM<sub>2.5</sub> exposure led to allergic inflammation and airway remodeling in animal models of allergic disease, which share many phenotypic features with asthma in humans. However, in studies of PM<sub>2.5</sub> CAPs, the response was dependent on concentration and source profile of the airshed.

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#### 5.1.2.5 Summary of Asthma Exacerbations

Recent epidemiologic studies strengthen the evidence for a relationship between short-term PM<sub>2.5</sub> exposure and asthma exacerbation in children. In particular, recent studies add evidence supporting associations between short-term PM<sub>2.5</sub> concentration and asthma hospital admissions, ED visits, and physician visits in children. Additional evidence of PM<sub>2.5</sub>-related increases in asthma symptoms, lung function decrements, and pulmonary inflammation is provided by recent panel studies in children with asthma. Findings were not entirely consistent, but overall several well-conducted studies measuring total personal exposure, residential outdoor concentration, and school outdoor PM<sub>2.5</sub> concentration observed associations with asthma-related effects. Evidence for a relationship between short-term PM<sub>2.5</sub> exposure and asthma exacerbation in adults continues to be inconsistent.

Evidence from experimental studies provides biological plausibility for associations seen in epidemiologic studies between short-term PM<sub>2.5</sub> exposure and asthma exacerbation. Although controlled

human exposure studies were inconsistent in showing effects on lung function and pulmonary inflammation in individuals with asthma, animal toxicological studies demonstrated allergic inflammation, enhanced serum IgE, and airway remodeling in animal models of allergic airway disease. These changes may lead to lung function decrements and respiratory symptoms, which were observed in epidemiology studies in relation to PM<sub>2.5</sub> exposure (Figure 5-1).

Across the indicators of asthma exacerbation, associations continue to be observed with 24-hour average PM<sub>2.5</sub> concentrations from the same day, from the few preceding days, or averaged over a few days (Section 5.1.10). Evidence does not clearly point to a stronger effect for a particular exposure lag. Recent epidemiologic studies add evidence from copollutant models that show that PM<sub>2.5</sub> associations are independent of a copollutant among NO<sub>2</sub>, CO, and O<sub>3</sub>. Based on more limited investigation, there is evidence that PM<sub>2.5</sub> associations may be modified by these copollutants and aeroallergens. Other copollutants largely are unexamined. While there are some results from copollutant models based on personal exposure measurements that may have less differential exposure measurement error, scarce application of copollutant models limits the ability to analyze potential for confounding. Thus, as in the 2009 ISA for PM (U.S. EPA, 2009), uncertainty remains in distinguishing an independent effect of PM<sub>2.5</sub> exposure on asthma exacerbation.

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### 5.1.3 Allergy Exacerbation

Animal toxicological studies reviewed in the 2009 PM ISA (U.S. EPA, 2009) provided evidence that PM<sub>2.5</sub> can facilitate delivery of allergenic material to the airways, promote allergic sensitization, and exacerbate allergic responses. Meanwhile, epidemiologic evidence was limited, with a single study reporting an association between short-term PM<sub>2.5</sub> concentrations and hospital admissions for allergic rhinitis in children in Turkey (Tecer et al., 2008). Recent evidence that PM<sub>2.5</sub> exposure enhances allergic inflammation in animal models of allergic airway disease, described in Section 5.1.2.4, not only supports PM<sub>2.5</sub>-related asthma exacerbation but also indicates that PM<sub>2.5</sub> exposure could affect respiratory responses in people with allergies, but not asthma. Several recent epidemiologic studies add to the evidence base, but do not consistently link short-term PM<sub>2.5</sub> exposure to allergy exacerbation in children or adults. Recent studies examined an array of outcomes, including allergy symptoms, and lung function changes and pulmonary inflammation in populations with allergies. Notably, lung function can decrease during an allergy exacerbation due to airway obstruction caused by Th2 cytokine mediated inflammation, making lung function and pulmonary inflammation relevant markers of allergy exacerbation.

While Tecer et al. (2008) found evidence of an association between short-term PM<sub>2.5</sub> concentrations and allergic rhinitis hospitalizations in children, Villeneuve et al. (2006) did not observe an association between short-term PM<sub>2.5</sub> and physician visits for allergic rhinitis in individuals 65 years of age and older in Toronto. The authors examined single-day lags ranging from 0 to 7 days and reported mostly null associations, with some small positive and negative associations depending on the lag day.

The comparative results of the studies may be indicative of age-related differences in allergic rhinitis sensitivity to PM<sub>2.5</sub>, but differences in study design and location make it difficult to draw conclusions. Other recent studies examined the relationship between short-term exposure to PM<sub>2.5</sub> and skin allergies, including urticaria (Kousha and Valacchi, 2015) and atopic dermatitis symptoms (Song et al., 2011). Kousha and Valacchi (2015) monitored ED visits for urticaria in relations to short-term PM<sub>2.5</sub> concentrations in Windsor, Ontario. The authors only analyzed single-day lags, ranging from 0 to 7 days prior to ED visits, and reported associations at lags 1 (OR = 1.07 [95% CI: 0.99, 1.16]), 2 (1.14 [1.04, 1.22]), and 3 (1.07 [0.99, 1.16]), with generally null results at other examined lag times. However, there are uncertainties in the urticaria results, because over 67% of the days included in the study period had less than two reported ED visits. Meanwhile, in a study of schoolchildren with atopic dermatitis in South Korea, PM<sub>2.5</sub> measured on the school rooftop was not associated with self-reported symptoms of itchy skin (Song et al., 2011).

As mentioned previously, lung function changes and pulmonary inflammation in populations with allergies may serve as markers of allergy exacerbation. In Mexico City, Barraza-Villarreal et al. (2008) examined the association between short-term PM<sub>2.5</sub> concentrations and several lung function and pulmonary inflammation metrics in schoolchildren with and without asthma. The authors reported that 72% of the 50 subjects without asthma were atopic, leading them to repeat the analysis in a subgroup of atopic children. In the subgroup analysis, PM<sub>2.5</sub> concentrations were positively associated with FeNO, a measure of airway inflammation, but no quantitative results were presented. The authors presumably did not observe similar associations with the other metrics examined in the main analysis, including IL-8, FEV<sub>1</sub>, FVC, and FEV<sub>25-75</sub>.

In summary, recent animal toxicological studies expand the existing evidence base, providing additional support for the biological plausibility of PM<sub>2.5</sub>-related allergy exacerbation. In contrast, a limited number of epidemiologic studies provide inconsistent evidence of an association across multiple endpoints, including a variety of allergic symptoms, and lung function changes and pulmonary inflammation in people with existing allergies.

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#### 5.1.4 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by destruction of alveolar tissue, airway remodeling, and airflow limitation. Reduced airflow is associated with decreased lung function, and clinical symptoms demonstrating exacerbation of COPD include cough, dyspnea, sputum production, and shortness of breath. Severe exacerbation can lead to ED visits or hospital admissions. The epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided evidence of consistent positive associations between short-term PM<sub>2.5</sub> exposure and increases in hospital admissions and ED visits for COPD. Experimental studies evaluated in the 2009 PM ISA and the 2004 PM AQCD (U.S. EPA, 2004) provide biological plausibility for effects seen in epidemiologic studies. A

1 limited number of controlled human exposure and animal toxicological studies demonstrated changes in  
2 lung function-related parameters, as well as lung injury and inflammation. Recent studies of the  
3 relationship between short-term PM<sub>2.5</sub> exposure and COPD exacerbation mainly examine hospital  
4 admissions and ED visits and are generally consistent in showing associations with PM<sub>2.5</sub>. A small body  
5 of studies expand the evidence base and show associations with respiratory symptoms and pulmonary  
6 inflammation in adults with COPD, in some cases with measures of personal PM<sub>2.5</sub>. Results for lung  
7 function changes are inconsistent. Thus, there is variable coherence among various endpoints linked to  
8 COPD exacerbation.

9 In addition to examining the relationship between short-term PM<sub>2.5</sub> exposure and COPD  
10 exacerbation, some epidemiologic studies often conduct analyses to assess whether the associations  
11 observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic  
12 studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically  
13 on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of  
14 copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure  
15 (Section 5.1.10.3), the role of season and temperature on PM<sub>2.5</sub> associations (Section 5.1.10.4), averaging  
16 time of PM<sub>2.5</sub> concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses  
17 (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily  
18 epidemiologic studies that conducted time-series or case-crossover analyses focusing on COPD hospital  
19 admissions and ED visits.

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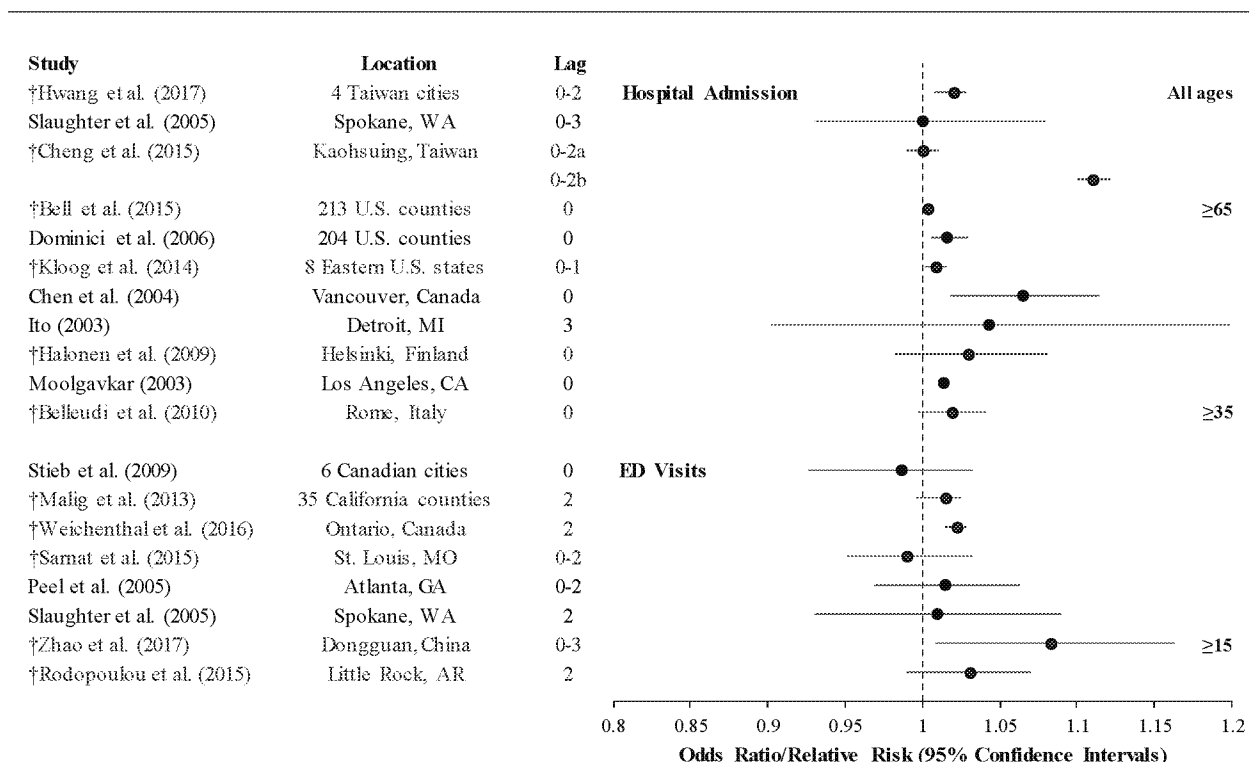
#### 5.1.4.1 Hospital Admissions and Emergency Department (ED) Visits

20 Associations between short-term exposure to PM<sub>2.5</sub> and hospital admissions and ED visits for  
21 COPD were generally positive among the multicity and single-city studies conducted in the U.S. and  
22 Canada and evaluated in the 2009 PM ISA (U.S. EPA, 2009). Multicity studies reviewed in the 2009 PM  
23 ISA examining PM<sub>2.5</sub> and hospital admissions for COPD reported both null [a Canadian study, (Stieb et  
24 al., 2009)] and positive [a U.S. study, (Dominici et al., 2006)] associations between COPD hospital  
25 admissions and PM<sub>2.5</sub>. The results from multicity studies were supported by single-city studies conducted  
26 in the U.S. and Canada that reported positive associations between short-term exposure to PM<sub>2.5</sub> and  
27 hospital admissions and ED visits for COPD.

28 Recent studies examining associations between short-term PM<sub>2.5</sub> exposure and COPD hospital  
29 admissions and ED visits generally support the positive associations reported in the 2009 PM ISA. These  
30 recent studies report positive associations across both multi- and single-city studies, especially for  
31 hospital admissions in populations 65 and older (see Figure 5-6, Table 5-8). However, most of the recent  
32 studies that examine short-term PM<sub>2.5</sub> exposure and COPD ED visits consist of single-city studies.

33 For each of the studies evaluated in this section, Table 5-8 presents the air quality characteristics  
34 of each city, or across all cities, the exposure assignment approach used, and information on copollutants

examined in each COPD hospital admission and ED visit study. Other recent studies of COPD hospital admissions and ED visits are not the focus of this evaluation because they did not address uncertainties and limitations in the evidence previously identified, and, therefore, do not directly inform the discussion of policy-relevant considerations detailed in Section 5.1.10. Additionally, many of these studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these studies can be found here: <https://hero.epa.gov/hero/particulate-matter>.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-6 Summary of associations between short-term PM<sub>2.5</sub> exposures and chronic obstructive pulmonary disease (COPD) hospital admissions and emergency department (ED) visits for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

**Table 5-8 Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.**

| Study  | Exposure Assessment                                 | Mean Concentration<br>µg/m <sup>3</sup>                                     | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup>                         | PM <sub>2.5</sub> Copollutant Model Results<br>and Correlations  |
|--|---|---|---|--|
| <b>Hospital admissions</b>   |   |   |   |  |
| †Bell et al. (2015)<br>213 U.S. counties<br>1999–2010<br>Older adults ≥65 yr   | Monitors in county averaged<br>Number per county NR | U.S.: 12.3<br>Northeast: 12.0<br>Midwest: 12.9<br>South: 12.4<br>West: 11.3 | Max U.S.: 20.2<br>Northeast: 16.4<br>Midwest: 16.5<br>South: 16.5<br>West: 20.2 | Correlations (r): NA<br>Copollutant models with: NA  |
| Dominici et al. (2006)<br>204 U.S. counties<br>†Peng et al. (2009b)<br>94 U.S. counties<br>1999–2002<br>Older adults ≥65 yr  | Monitors in county averaged<br>Number per county NR | 13.4  | 75th: 15.2  | Correlations (r): NA<br>Copollutant models with: NA  |
| †Kloog et al. (2014)<br>New York, New Jersey,<br>Pennsylvania, Maryland,<br>Delaware, Virginia, West<br>Virginia, Washington, DC<br>2000–2006<br>Older adults ≥65 yr | Satellite-monitor hybrid model                      | Urban: 12.8<br>Rural: 11.5  | 75th<br>Urban: 16.7<br>Rural: 14.2<br>Max<br>Urban: 96.1<br>Rural: 95.9         | Correlations (r): NA<br>Copollutant models with: NA  |
| Chen et al. (2004)<br>Vancouver, Canada<br>1995–1999<br>Older adults ≥65 yr  | NR  | 7.7   | 75th: 9.0<br>Max: 32  | Correlations (r): NA<br>Copollutant models with: O <sub>3</sub> , NO <sub>2</sub> ,<br>CO, SO <sub>2</sub> |

**Table 5-8 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.**

| Study   | Exposure Assessment                       | Mean Concentration<br>µg/m <sup>3</sup> | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | PM <sub>2.5</sub> Copollutant Model Results<br>and Correlations  |
|---|---|---|---|--|
| <u>Ito (2003)</u><br>Detroit, MI<br>1992–1994<br>Older adults, age NR                   | One monitor in Windsor, Ontario           | 18                                      | 75th: 21<br>95th: 42                                    | Correlations (r): NA<br>Copollutant models with: NA  |
| <u>†Hälonen et al. (2009a)</u><br>Helsinki, Finland<br>1998–2004<br>Older adults ≥65 yr | Two monitors                              | Median: 8.8                             | 75th: 11.0<br>Max: 41.5                                 | Correlation (r): 0.43 O <sub>3</sub> .<br>Copollutant models with: O <sub>3</sub>  |
| <u>Moolgavkar (2003)</u><br>Los Angeles, CA<br>1987–1995<br>All adults                  | Monitors in city<br>Number of monitors NR | NR                                      | NR  | Correlation (r): NA<br>Copollutant models with: CO, SO <sub>2</sub> ,<br>NO <sub>2</sub> .   |
| <u>†Kim et al. (2012)</u><br>Denver, CO<br>2003–2007<br>All adults                      | One monitor                               | 8.0                                     | Max: 59.4   | Correlation (r): 0.30 O <sub>3</sub> , 0.26 NO <sub>2</sub> ,<br>0.23 CO, 0.23 SO <sub>2</sub><br>Copollutant models with: NA  |
| <u>†Liu et al. (2016)</u><br>Greater Houston area, TX<br>2008–2013<br>All adults        | Four monitors averaged from one<br>county | 12.0                                    | 90th: 18.5  | Correlations (r): NA<br>Copollutant models with: NA  |
| <u>†Cheng et al. (2015)</u><br>Kaohsiung, Taiwan<br>2006–2010<br>All adults             | Six monitors averaged                     | Median: 44.3                            | 75th: 61.9<br>Max: 144                                  | Correlation (r): 0.42 O <sub>3</sub> , 0.80 NO <sub>2</sub> ,<br>0.81 CO, 0.25 SO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> , NO <sub>2</sub> ,<br>CO, SO <sub>2</sub> |

**Table 5-8 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.**

| Study  | Exposure Assessment  | Mean Concentration<br>µg/m <sup>3</sup>                              | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | PM <sub>2.5</sub> Copollutant Model Results<br>and Correlations   |
|--|--|--|---|---|
| †Zhao et al. (2016)<br>Dongguan, China<br>2013–2015<br>All adults  | Five monitors averaged   | 42.6   | 75th: 56.8<br>Max: 193                                  | Correlation (r): 0.40 O <sub>3</sub> , 0.67 NO <sub>2</sub> ,<br>0.69 SO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> , SO <sub>2</sub> ,<br>NO <sub>2</sub>   |
| †Belleudi et al. (2010)<br>Rome, Italy<br>2001–2005  | One monitor, 2 km from city center   | 22.8   |   | Correlation (r): 0.84 PM <sub>10</sub><br>Copollutant models with: NA   |
| <b>ED visits</b>   |  |  |   |   |
| †Weichenthal et al. (2016)<br>15 cities Ontario, Canada<br>2004–2011<br>All ages   | Nearest monitor to<br>population-weighted zip code centroid<br>or single available monitor | 7.1  | Max: 56.8   | Correlation (r): <0.42 NO <sub>2</sub><br>Copollutant models with: O <sub>3</sub>   |
| †Sarnat et al. (2015)<br>St. Louis, MO (eight Missouri<br>counties, eight Illinois counties)<br>2001–2003<br>All adults                        | One monitor  | 18.0   | 75th: 22.7<br>Max: 48.7                                 | Correlation (r): 0.23 O <sub>3</sub> , 0.35 NO <sub>2</sub> ,<br>0.25 CO, 0.08 SO <sub>2</sub> .<br>Copollutant models with: NA   |
| †Krall et al. (2016)<br>Atlanta, GA, 1999–2009<br>Birmingham, AL, 2004–2010<br>St. Louis, MO, 2001–2007<br>Dallas, TX, 2006–2009<br>All adults | One monitor, each city   | Atlanta: 15.6<br>Birmingham: 17.0<br>St. Louis: 13.6<br>Dallas: 10.7 | NR  | Correlation (r): 0.57 O <sub>3</sub> , 0.39 NO <sub>2</sub><br>Atlanta, 0.42 O <sub>3</sub> , –0.15 NO <sub>2</sub> Dallas,<br>0.29 O <sub>3</sub> , 0.29 NO <sub>2</sub> St. Louis.<br>Copollutant models with: NA |

**Table 5-8 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for chronic obstructive pulmonary disease.**

| Study   | Exposure Assessment   | Mean Concentration<br>µg/m <sup>3</sup>   | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup>   | PM <sub>2.5</sub> Copollutant Model Results<br>and Correlations  |
|---|---|---|---|--|
| Peel et al. (2005)<br>Atlanta, GA<br>1998–2000<br>All adults  | One monitor   | 19.2  | 90th: 32.3  | Correlations (r): NA<br>Copollutant models with: NA  |
| †Rodopoulou et al. (2015)<br>Little Rock, AR<br>2002–2012<br>Adults >15 yr  | One monitor   | 12.4  | 75th: 15.6  | Correlation (r): 0.33 O <sub>3</sub><br>Copollutant models with: O <sub>3</sub>  |
| †Malig et al. (2013);<br>†Ostro et al. (2016)<br>35 or 8 California counties<br>2005–2008<br>All adults                               | Nearest monitor   | 35 counties: 5.2–19.8<br>8 counties: 16.5 overall   | NR  | Correlations (r): NA<br>Copollutant models with: NA  |
| Stieb et al. (2009)<br>Halifax, Montreal, Toronto,<br>Ottawa, Edmonton, Vancouver,<br>Canada<br>1992–2003 across cities<br>All adults | One monitor Halifax, Ottawa,<br>Vancouver; three Edmonton; seven<br>Montreal, Toronto | Halifax: 9.8<br>Montreal: 8.6<br>Toronto: 9.1<br>Ottawa: 6.7<br>Edmonton: 8.5<br>Vancouver: 6.8 | 75th, Halifax: 11.3<br>Montreal: 10.9<br>Toronto: 11.9<br>Ottawa: 8.7<br>Edmonton: 10.9<br>Vancouver: 8.5 | Correlation (r): –0.05 to 0.62 O <sub>3</sub> ,<br>0.27–0.51 NO <sub>2</sub> , 0.01–0.42 CO,<br>0.01–0.55 SO <sub>2</sub> .<br>Copollutant models with: NA |
| <b>Hospital admissions and ED visits</b>  |   |   |   |  |
| Slaughter et al. (2005)<br>Spokane, WA<br>1995–1999   | One monitor   | NR  | 90th: 20.2  | Correlation (r): 0.62 CO<br>Copollutant models with: NA  |

Avg = average, CO = carbon monoxide, IQR = interquartile range, max = maximum, NO<sub>2</sub> = nitrogen dioxide, NR = not reported, O<sub>3</sub> = ozone, PM<sub>2.5</sub> = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; r = correlation coefficient; R<sup>2</sup> = coefficient of determination, RR = relative risk, SD = standard deviation, SO<sub>2</sub> = sulfur dioxide.

†Studies published since the 2009 PM ISA.

#### 5.1.4.1.1 Hospital Admissions

Several recent multicity studies conducted in the U.S. examined associations between short-term PM<sub>2.5</sub> exposure and COPD hospital admissions in individuals 65 years and older. In a multicity study conducted in the Mid-Atlantic region of the U.S., [Kloog et al. \(2014\)](#) examined associations between short-term PM<sub>2.5</sub> exposure and COPD hospital admissions by assigning exposure using a novel prediction model that combined land use regression with surface measurements of PM<sub>2.5</sub> concentration and satellite aerosol optical depth, which was also employed in a previous study conducted in New England ([Kloog et al., 2012](#)). The authors reported a 0.91% (95% CI: 0.18, 1.64) increase in COPD hospital admissions at model lag 0–1 days.

[Bell et al. \(2015\)](#) also examined COPD hospital admissions in adults ages 65 and older in a multicounty time-series analysis conducted in 213 U.S. counties. However, unlike [Kloog et al. \(2014\)](#), where exposures were assigned using model predictions, [Bell et al. \(2015\)](#) assigned exposures through PM<sub>2.5</sub> data retrieved from ambient monitors in each county. The authors reported a 0.34% (95% CI: –0.05, 0.74) increase in COPD hospital admissions at lag 0, which is smaller in magnitude than the association observed in [Kloog et al. \(2014\)](#), but may reflect the different exposure assignment approaches (Section 3.4.4.1). Consistent with the U.S. multicity studies, [Hwang et al. \(2017\)](#) also reported a positive association of 2% ([95% CI: 0.8, 2.9]; lag 0–2) with COPD hospital admissions in a study of four cities in southwestern Taiwan focusing on people of all ages.

Several recent single-city studies in the U.S. reported inconsistent evidence of an association between short-term exposure to PM<sub>2.5</sub> and hospital admissions for COPD. [Kim et al. \(2012\)](#) found no evidence of an association with COPD hospital admissions in Denver, Colorado (quantitative results not reported). Several single-city international studies examined the association with COPD hospital admissions and support the evidence reported in the U.S. multicity studies. A single-city study conducted in Rome, Italy focusing on adults aged 35 years and older investigated the association between PM<sub>2.5</sub> and COPD hospital admissions in a case-crossover analysis ([Belleudi et al., 2010](#)). Effects were assessed at several single- (0–6) and multiday lags (0–1, 0–2, 0–5 and 0–6 days). The association for PM<sub>2.5</sub> at a 0-day lag was positive but with wide confidence intervals (1.88% [95% CI: –0.27, 4.09]). The evidence observed using a shorter distributed lag is consistent with the lag structure of associations observed in the other COPD hospital admission studies, although in many instances the lags examined were selected a priori. In a similar fashion, [Halonen et al. \(2009a\)](#) observed a 3% increase (95% CI: –1.9, 8.1) at lag 0 in a model adjusted for O<sub>3</sub> for hospital admissions in Helsinki, Finland, but with a wide confidence interval due to the low count of hospital admissions compared to other studies. [Cheng et al. \(2015\)](#), examining hospital admissions in a case-crossover study in Kaohsiung, Taiwan, found no association between PM<sub>2.5</sub> at a 0–2-day lag (RR 1.00, 95% CI: 0.98, 1.03).

#### 5.1.4.1.2 Emergency Department (ED) Visits

Several recent multicity studies conducted in the U.S. examined associations between short-term PM<sub>2.5</sub> exposure and COPD ED visits. In a multicity study conducted in 35 California counties, [Malig et al. \(2013\)](#) examined the association between short-term PM<sub>2.5</sub> exposures and respiratory ED visits, including COPD. In a time-stratified case-crossover analysis, the authors examined single-day lags and reported positive associations at lags 1 and 2 days, with the most precise estimate at lag 2 (1.47% [95% CI: 0.40, 2.6]). In a copollutant model with PM<sub>10-2.5</sub>, the PM<sub>2.5</sub> association was relatively unchanged (1.58% [95% CI: 0.56, 2.62]) [[Malig et al. \(2013\)](#) and supplemental data file available on HERO]. The positive association observed in the multicounty study conducted by [Malig et al. \(2013\)](#) is supported by a study conducted in Little Rock, AR ([Rodopoulou et al., 2015](#)) that observed a 3.08% increase (95% CI: -0.98, 7.30) in COPD ED visits at lag 2. [Rodopoulou et al. \(2015\)](#) also examined the PM<sub>2.5</sub>-COPD ED visits association in a copollutant model with O<sub>3</sub> and reported that the association remained positive, but confidence intervals increased in size (2.86% [95% CI: -1.35, 7.24]). A multicity case-crossover study of 15 cities in Ontario, Canada found an increase on the same order (2.2%) with higher precision (95% CI: 1.4, 2.9) than ([Rodopoulou et al., 2015](#)) using a 3-day mean lag structure.

In contrast, [Sarnat et al. \(2015\)](#) in a time-series study of PM<sub>2.5</sub> and cardiorespiratory ED visits in the St. Louis Missouri-Illinois (MO-IL) metropolitan area also reported no evidence of an association with COPD ED visits. The authors used 3-day unconstrained distributed lag models (i.e., lag 0–2) to allow for comparison of relationships among the multiple components and outcomes with potentially different lag structures. There was no evidence of an association between PM<sub>2.5</sub> and COPD ED visits (RR: 0.99 [95% CI: 0.95, 1.03]).

#### 5.1.4.1.3 Summary of Chronic Obstructive Pulmonary Disease (COPD) Hospital Admissions and Emergency Department (ED) Visits

Consistent with the 2009 PM ISA ([U.S. EPA, 2009](#)), several recent studies examined COPD hospital admissions and ED visits and report generally positive associations with PM<sub>2.5</sub>, with more recent multicity studies focusing on hospital admissions for older individuals (i.e., 65 years of age and older). Recent multicity studies conducted in the U.S., as well as single-city studies, that focused on individuals 65 years of age and older reported positive associations between short-term PM<sub>2.5</sub> exposure and COPD hospital admissions. Associations of short-term PM<sub>2.5</sub> exposure and ED visits, although generally positive, were less precise due to most studies being conducted in individual cities. The results from the studies evaluated in this section are supported by a recent meta-analysis of 12 studies, some of which were reviewed in the 2009 PM ISA that reported a 3.1% (95% CI: 1.6,4.6) increase in COPD hospital admissions ([Li et al., 2015a](#)). As detailed in [Section 5.1.10.1](#), the assessment of potential copollutant confounding in studies of COPD hospital admissions and ED visits was limited, but provided evidence that associations were relatively unchanged in copollutant models. Additionally, although not extensively examined, studies generally provide evidence of larger associations in the cold or winter season compared

to warmer months (Section 5.1.10.4.1). However, it should be noted studies that examined seasonal patterns of associations did not examine potential copollutant confounding by season.

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#### 5.1.4.2 Respiratory Symptoms and Medication Use

A single study reviewed in the 2009 PM ISA (U.S. EPA, 2009) examined respiratory symptoms and medication use in adults with COPD and observed inconsistent evidence of an association with PM<sub>2.5</sub> across three single-day lags (Silkoff et al., 2005). A limited number of recent studies available for review followed populations comprised of adults with moderate or severe COPD. The results were not entirely consistent, though there was some evidence to indicate associations between PM<sub>2.5</sub> concentrations and increases in respiratory symptoms in adults with COPD. Study-specific details, air quality characteristics, and select results from these studies are highlighted in Table 5-9. Wu et al. (2016) examined the self-reported occurrence of several respiratory symptoms in relation to short-term PM<sub>2.5</sub> concentrations in a panel study of 23 adults in Beijing. The authors reported associations between most multiday (2–7) average PM<sub>2.5</sub> concentrations and sore throat, cough, sputum, wheeze, and dyspnea symptoms. Similarly, in a panel of 29 adults in Mexico City, total personal PM<sub>2.5</sub> exposure was associated with cough and phlegm, though not wheeze (Cortez-Lugo et al., 2015). A notable limitation of the study was high loss to follow-up, with only 4 of the 29 subjects completing all three of the 2-week study phases. In contrast, in a study of adults in Worcester, MA, PM<sub>2.5</sub> was associated with a decrease in COPD exacerbations, defined as a worsening of respiratory symptoms (Devries et al., 2016). Studies accounted for potential confounding by temperature, season, and time trend and also adjusted for subject characteristics such as COPD severity, race, atopic status, and comorbidity. Few studies examined any copollutants. Associations of PM<sub>2.5</sub> concentrations with wheeze and dyspnea persisted with adjustment for NO<sub>2</sub> or SO<sub>2</sub> in (Wu et al., 2016). However, correlations for PM<sub>2.5</sub> with NO<sub>2</sub> and SO<sub>2</sub> were high ( $r = 0.80, 0.68$ ).

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#### 5.1.4.3 Lung Function Changes in Adults with Chronic Obstructive Pulmonary Disease (COPD)

##### 5.1.4.3.1 Epidemiologic Studies

In the 2009 PM ISA (U.S. EPA, 2009), results from a limited number of epidemiologic studies indicated an association between PM and decreased FEV<sub>1</sub> in adults with COPD (Trenga et al., 2006; Ebelt et al., 2005). A few recent studies also evaluated lung function changes in populations with COPD and the results were inconsistent (Table 5-9). Recent studies used trained technicians to measure lung function, but the frequency of measurements varied from daily (Hsu et al., 2011) to less than once per week (Cortez-Lugo et al., 2015). Total personal PM<sub>2.5</sub> exposure was associated with decreased PEF in adults with COPD in Mexico City, who spent more than 90% of their time indoors (Cortez-Lugo et al.,

1 2015). As discussed previously, there was high loss to follow-up in this study. Associations were  
2 observed with 2-day average exposures lagged 2 or 3 days but not 0 or 1 days. In a small panel study of  
3 adults with COPD in New York City, ambient PM<sub>2.5</sub> concentrations were associated with decreases in  
4 PEF at lag 1, but increases in PEF at lag 0 (Hsu et al., 2011). Given the short sampling period (12 days)  
5 and relatively small sample size (nine participants), the interpretability of the results is limited.

**Table 5-9 Epidemiologic studies of PM<sub>2.5</sub> and respiratory symptoms, lung function, and pulmonary inflammation in adults with chronic obstructive pulmonary disease.**

| Study   | Study Population  | Exposure Assessment<br>Concentration $\mu\text{g}/\text{m}^3$   | Single Pollutant Effect Estimate<br>95% CI <sup>a</sup>   | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations   |
|---|---|---|---|---|
| †Chi et al. (2016)<br>Southwestern Taiwan<br>2014–2016          | N = 19, 68% severe COPD<br>Questionnaire every 2 mo for 1 yr<br>73% follow-up participation   | Home outdoor<br>Three measures for 1-min<br>Mean: 120   | Score for PM <sub>2.5</sub> >35 vs. $\leq 35 \mu\text{g}/\text{m}^3$<br>Wheeze: 1.46, $p < 0.01$<br>Phlegm: $-0.22$ , $p > 0.05$<br>Dyspnea: $0.84$ , $p > 0.05$<br>Activity limitation: $-0.84$ , $p > 0.05$ | Correlation ( $r$ ): NA<br>Copollutant models with:<br>NA   |
| †Cortez-Lugo et al. (2015)<br>Mexico City, Mexico<br>Years NR   | N = 29, mean 37% predicted FEV <sub>1</sub><br>Daily diary for three 12-day periods<br>Recruited from clinic<br>62% completed two or three sessions<br>90% time spent indoors | Total personal<br>2-day avg<br>Mean: 39   | Phlegm, lag 2: 1.23 (0.98, 1.54)<br>Cough, lag 2: 1.33 (1.05, 1.69)<br>Nighttime PEF (L/min)<br>Lag 1: 0.16 ( $-2.3$ , 2.6)<br>Lag 2: $-3.0$ ( $-5.7$ , $-0.3$ )  | Correlation ( $r$ ): NA<br>Copollutant models with:<br>NA   |
| †Devries et al. (2016)<br>Worcester, MA<br>2011–2012            | N = 168, 68% severe COPD<br>Calls to nurse on symptom onset<br>Recruited from clinic<br>No information on participation rate  | Three monitors averaged<br>Mean: 8.6<br>Max: 37.0   | Any symptom, lag 1: 0.54 (0.28, 1.10)   | Correlation ( $r$ ): (seasonal range) 0.41–0.83 NO <sub>2</sub> ,<br>0.30–0.79 SO <sub>2</sub><br>Copollutant models with:<br>NO <sub>2</sub> and SO <sub>2</sub>                   |
| †Wu et al. (2016)<br>Beijing, China<br>Jan–Apr, Aug–Sep<br>2014 | N = 23, 81% moderate/severe COPD<br>Daily diary for 11–81 days<br>5–21 weekly eNO measures<br>Recruited from clinic<br>96% completed one or two test periods                  | One monitor<br>1.6–8.8 km from homes<br>24-h avg<br>Median, 75th<br>Period 1: 96.5, 149<br>Period 2: 65.5, 92.0 | Dyspnea, lag 0–4: 1.20 (1.10, 1.29)<br>Sputum, lag 0–4: 1.06 (1.0, 1.13)<br>Cough, lag 0–4: 1.05 (0.99, 1.14)<br>eNO, lag 0–4: 1.7% (0.6, 2.8)  | Correlation ( $r$ ): 0.80 NO <sub>2</sub> ,<br>0.68 SO <sub>2</sub> , 0.84 PM <sub>10</sub><br>Copollutant models with:<br>NO <sub>2</sub> , SO <sub>2</sub> , and PM <sub>10</sub> |

**Table 5-9 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory symptoms, lung function, and pulmonary inflammation in adults with chronic obstructive pulmonary disease.**

| Study   | Study Population   | Exposure Assessment<br>Concentration µg/m <sup>3</sup>  | Single Pollutant Effect Estimate<br>95% CI <sup>a</sup>   | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations |
|---|--|---|---|---|
| Trenga et al. (2006)<br>Seattle, WA<br>1999–2002        | N = 24, mean 56% predicted FEV <sub>1</sub><br>Daily FEV <sub>1</sub> for 36 sessions, 5–10 days each<br>Supervised spirometry<br>Recruited from clinics, senior centers, retirement homes | Total personal, fixed-site monitor, and home outdoor<br>24-h avg<br>Medians, 75th<br>Total personal: 11.3, 16<br>Monitor: 11.2, 16.9<br>Home outdoor: 9.6, 14.8   | Change in FEV <sub>1</sub> (ml), lag 1<br>Total personal: –19 (–74, 36)<br>Fixed-site monitor: –71 (–118, –23)<br>Home outdoor: –45 (–103, 12)              | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA     |
| Ebelt et al. (2005)<br>Vancouver, Canada<br>1998        | N = 16, light/moderate COPD<br>5–7 FEV <sub>1</sub> measures, every 1.5 week<br>Supervised spirometry<br>No information on participation rate  | Personal exposure, five monitors<br>24-h avg<br>Ambient exposure estimated from total personal SO <sub>4</sub> <sup>2–</sup> , air infiltration, time-activity<br>Mean, max<br>Total personal: 18.5, 90.9<br>Ambient exposure: 7.9, 21.3<br>Monitor: 11.4, 28.7 | Change in FEV <sub>1</sub> (ml), lag 0<br>Total personal: –0.39 (–14, 14)<br>Ambient exposure: –66 (–124, –13)<br>Monitor: –27 (–88, 34)                    | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA     |
| †Hsu et al. (2011)<br>New York, NY<br>Nov 2002–Mar 2003 | N = 9<br>Recruited from clinics<br>Daily FEV <sub>1</sub> and PEF for 12 days<br>Supervised spirometry<br>No information on participation rate   | One monitor within 4.8 km of home<br>24-h avg<br>Concentrations NR  | New York: Negative association of PEF with PM <sub>2.5</sub> at monitor at lag 1 but positive association of PEF with PM <sub>2.5</sub> at monitor at lag 0 | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA     |

Avg = average, COPD = chronic obstructive pulmonary disease, eNO = exhaled nitric oxide, IQR = interquartile range, FEV<sub>1</sub> = forced expiratory volume in 1 second, max = maximum, NO<sub>2</sub> = nitrogen dioxide, NR = not reported, PEF = peak expiratory flow, PM<sub>2.5</sub> = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm; *r* = correlation coefficient; R<sup>2</sup> = coefficient of determination, RR = relative risk, SD = standard deviation, SO<sub>2</sub> = sulfur dioxide, SO<sub>4</sub><sup>2–</sup> = sulfate.

<sup>a</sup>Unless otherwise specified, effect estimates are standardized to a 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub>.

†Studies published since the 2009 PM ISA.

#### 5.1.4.3.2 Controlled Human Exposure Studies

Two studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provide limited evidence for decreased lung function among subjects with COPD exposed to PM<sub>2.5</sub> (Gong et al., 2005; Gong et al., 2004). Gong et al. (2004) reported decreases in oxygen saturation among elderly COPD patients, although results were more consistent in elderly subjects without COPD; the authors reported no effects on spirometric measures of lung function. The association between PM<sub>2.5</sub> and decreased oxygen saturation in COPD patients was confirmed in Gong et al. (2005).

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#### 5.1.4.4 Subclinical Effects Underlying Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

##### 5.1.4.4.1 Epidemiologic Studies

A limited number of studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) reported evidence of an association between short-term PM<sub>2.5</sub> concentrations and pulmonary inflammation in adults with COPD. Studies examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation, a key characteristic of COPD. Additionally, there is evidence that eNO increases during acute COPD exacerbation (Perng and Chen, 2017). Small panel studies of older adults in Steubenville, OH (Adamkiewicz et al., 2004) and Seattle, WA, (Jansen et al., 2005) reported increases in eNO associated with 24-hour average PM<sub>2.5</sub> concentrations measured at a single fixed-site monitor or outside of participants residences, respectively.

Information from the few available recent studies continues to support a relationship between PM<sub>2.5</sub> and increases in pulmonary inflammation in adults with COPD. Recent studies evaluated panels of older adults with COPD in Shanghai (Chen et al., 2015b) and Beijing, China (Wu et al., 2016). In both studies, PM<sub>2.5</sub> was measured at a single fixed-site monitor located within 4 km (Chen et al., 2015b) or 1.6–8.8 km (Wu et al., 2016) of subjects' residences, but information on the variability in PM<sub>2.5</sub> concentrations in the study areas was not reported. Chen et al. (2015b) observed eNO increases consistent with increases in PM<sub>2.5</sub> concentrations at 7–12-hour, 13–24-hour, 1-, 2-, and 3–7-day lags. Supporting these findings, the authors also reported associations between PM<sub>2.5</sub> and decreased methylation of the inducible nitric oxide synthase gene promoter that demonstrated the largest decrements at lag 0–6 hour. Lower methylation is associated with increased gene expression of inducible nitric oxide synthase which mediates production of nitric oxide. Wu et al. (2016) did not examine hourly lags but reported associations between eNO and cumulative average PM<sub>2.5</sub> concentrations ranging from 1 to 7 days. eNO associations were robust to adjustment for NO<sub>2</sub> but attenuated and no longer positive in two-pollutant models including SO<sub>2</sub> (Wu et al., 2016). However, there were high correlations of PM<sub>2.5</sub> with NO<sub>2</sub> and

SO<sub>2</sub> ( $r = 0.80, 0.68$ ). While these studies provide additional support to the previously limited evidence of an association between PM<sub>2.5</sub> exposure and pulmonary inflammation in adults with COPD, uncertainties remain in attributing the observed increases in pulmonary inflammation to PM<sub>2.5</sub> exposure, similar to findings for other indicators of COPD exacerbation.

#### 5.1.4.4.2 Controlled Human Exposure Studies

In the 2009 PM ISA (U.S. EPA, 2009), a limited number of studies investigated PM<sub>2.5</sub>-induced health effects in adults with COPD. (Gong et al., 2004) and Gong et al. (2005) found a decrease in columnar epithelia cells ( $p < 0.01$ ) following short-term exposure to PM<sub>2.5</sub>. This effect was more pronounced in healthy subjects compared to those with COPD.

#### 5.1.4.4.3 Animal Toxicological Studies

While no additional toxicological studies on the effects of PM on COPD have become available in recent years, the 2004 PM AQCD (U.S. EPA, 2004) reported several studies which examined the effects of multiday exposure to PM<sub>2.5</sub> CAPs in rats with experimentally induced bronchitis, an animal model of COPD. Changes in tidal volume, BALF injury markers (protein, albumin, and N-acetyl glutaminidase), and numbers of BALF neutrophils and lymphocytes were greater in bronchitic rats compared to nonbronchitic rats exposed to PM<sub>2.5</sub> CAPs from Boston (Saldiva et al., 2002; Clarke et al., 1999) and Research Triangle Park, NC (Kodavanti et al., 2000).

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#### 5.1.4.5 Summary of Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Recent studies generally support an association between short-term increases in PM<sub>2.5</sub> concentration and exacerbation of COPD. Recent studies expand on the array of COPD-related outcomes and add coherence for the observations of PM<sub>2.5</sub>-related increases in COPD-related hospital admissions and ED visits. Overall, evidence links short-term PM<sub>2.5</sub> exposure to COPD hospital admissions and ED visits. These findings are supported by recent observations of PM<sub>2.5</sub>-related pulmonary inflammation; evidence for PM<sub>2.5</sub>-related symptoms and decreases in lung function is less consistent. A strength of these studies is their assessment of personal PM<sub>2.5</sub> exposures. Overall, copollutant confounding was not adequately examined. Thus, it is unclear the extent to which the results can be attributed specifically to PM<sub>2.5</sub> exposure. However, experimental studies in individuals with COPD and in an animal model of COPD support an independent effect of short-term PM<sub>2.5</sub> exposure on exacerbation of COPD. Changes in lung function-related parameters (oxygen saturation and tidal volume), as well as lung injury and inflammation were observed following short-term PM<sub>2.5</sub> CAPs exposure and provide biological plausibility for the findings of epidemiologic studies (Figure 5-1).

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## 5.1.5 Respiratory Infection

1 The respiratory tract is protected from exogenous pathogens by lung host defenses that include  
2 mucociliary clearance, pathogen detoxification, and clearance by alveolar macrophages, as well as innate  
3 and adaptive immunity. Impairment of these defense mechanisms can increase the risk of respiratory  
4 infection. The 2009 PM ISA (U.S. EPA, 2009) described evidence supporting PM<sub>2.5</sub>-related respiratory  
5 infection but there was uncertainty due to a small evidence base relative to those for other respiratory  
6 effects. Previous epidemiologic studies consistently observed associations between PM<sub>2.5</sub> concentrations  
7 and hospital admissions or ED visits for indices aggregating various respiratory infections, particularly in  
8 U.S. and European cities. Findings from a limited number of studies also supported associations with  
9 pneumonia. In the 2004 PM AQCD and the 2009 PM ISA, controlled human exposure studies were not  
10 available to assess coherence, but an animal toxicological study demonstrated increased susceptibility to  
11 pneumonia infection and altered macrophage function following exposure to PM<sub>2.5</sub>. Hospital admissions  
12 and ED visits comprise most of the epidemiologic evidence of respiratory infections and consistently  
13 indicate associations for PM<sub>2.5</sub> concentrations with multiple respiratory infections grouped together but  
14 not individually with pneumonia. Interpretation of the evidence, however, is complicated by the variety of  
15 respiratory infection outcomes examined.

16 In addition to examining the relationship between short-term PM<sub>2.5</sub> exposure and respiratory  
17 effects, some epidemiologic studies often conduct analyses to assess whether the associations observed  
18 are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not  
19 discussed within this section, but evaluated in an integrative manner and focuses specifically on those  
20 analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant  
21 confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role  
22 of season and temperature on PM<sub>2.5</sub> associations (Section 5.1.10.4), averaging time of PM<sub>2.5</sub>  
23 concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses  
24 (Section 5.1.10.6). The studies that inform these issues and evaluated within these sections are primarily  
25 epidemiologic studies that conducted time-series or case-crossover analyses focusing on respiratory  
26 infection hospital admissions and ED visits.

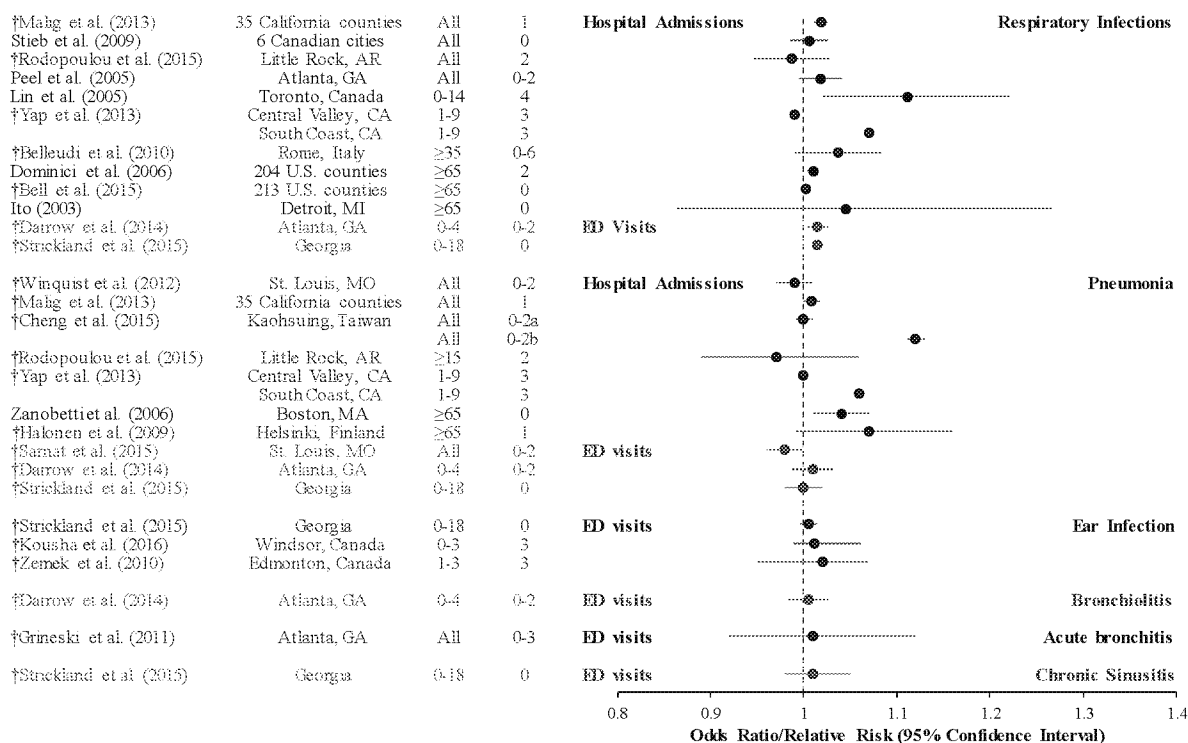
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### 5.1.5.1 Hospital Admissions and Emergency Department (ED) Visits

27 Associations between short-term PM<sub>2.5</sub> exposure and hospital admissions and between short-term  
28 PM<sub>2.5</sub> exposure and ED visits for respiratory infections were consistently observed among multicity  
29 studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), although the type of respiratory infection  
30 examined varied across the studies (i.e., acute bronchitis, bronchiolitis, and pneumonia). Several multicity  
31 studies reported associations between short-term PM<sub>2.5</sub> exposure and pneumonia and acute bronchitis in  
32 children. The overall evidence base examining short-term PM<sub>2.5</sub> exposure and hospital admissions and ED  
33 visits for respiratory infections expanded considerably since the 2009 PM ISA. These recent studies

1 report generally positive associations between PM<sub>2.5</sub> and hospital admissions and ED visits for  
2 pneumonia, ear infections, and all respiratory infections grouped together (see [Figure 5-7](#), Table 5-10). As  
3 in the 2009 PM ISA, respiratory infections when combined capture a range of outcomes (pneumonia, ear  
4 infections, bronchiolitis, sinusitis), with studies primarily focusing on children.

5 For each of the studies evaluated in this section, Table 5-10 presents the air quality characteristics  
6 of each city, or across all cities, the exposure assignment approach used, and information on copollutants  
7 examined in each respiratory infection hospital admission and ED visit study. Other recent studies of  
8 respiratory infection hospital admissions and ED visits are not the focus of this evaluation because they  
9 did not address uncertainties and limitations in the evidence previously identified, and therefore, do not  
10 directly inform the discussion of policy-relevant considerations detailed in [Section 5.1.10](#). Additionally,  
11 many of these studies were conducted in small single cities, encompassed a short study duration, or had  
12 insufficient sample size. The full list of these studies can be found here:  
13 <https://hero.epa.gov/hero/particulate-matter>.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-7 Summary of associations between short-term PM<sub>2.5</sub> exposures and respiratory infection hospital admissions and emergency department (ED) visits for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

**Table 5-10 Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for respiratory infection.**

| Study  | Exposure Assessment   | Outcome Assessment  | Mean Concentration<br>µg/m <sup>3</sup>  | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup>  | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations  |
|--|---|---|--|--|--|
| <b>Children</b>  |   |   |  |  |  |
| <u>Lin et al. (2005)</u><br>Toronto, Canada<br>1998–2001   | Four monitors averaged  | Hospital admissions<br>URI + LRI                                    | 9.6  | 75th: 12.3<br>Max: 50.5  | Correlation ( <i>r</i> ): 0.56 O <sub>3</sub> , 0.48<br>NO <sub>2</sub> , 0.10 CO, 0.47 SO <sub>2</sub><br>Copollutant models with: NA |
| <u>†Yap et al. (2013)</u><br>12 counties, Central Valley<br>and South Coast, CA<br>2000–2005                 | Monitors in county averaged<br>Number per county NR.<br>73 monitors total in state. | Hospital admissions<br>ARI and pneumonia                            | 12.8 Sacramento to<br>24.6 Riverside   | NR   | Correlation ( <i>r</i> ): 0.25 O <sub>3</sub> .<br>Copollutant models with: NA   |
| <u>†Darrow et al. (2014)</u><br>Atlanta, GA<br>1993–2010   | 11 monitors combined for<br>each census tract                                       | ED visits<br>URI and pneumonia                                      | 14.1   | 75th: 17.8<br>95th: 27.4<br>Max: 75.2  | Correlation ( <i>r</i> ): 0.30 O <sub>3</sub> , 0.41<br>NO <sub>2</sub> , 0.45 CO<br>Copollutant models with: NA                       |
| <u>†Xiao et al. (2016);</u><br><u>†Strickland et al. (2015)</u><br>Georgia, whole state<br>2002–2008 or 2010 | Fuse-CMAQ; satellite-monitor<br>model   | ED visits<br>URI, pneumonia, ear<br>infection, chronic<br>sinusitis | Fuse-CMAQ<br>Mean<br>13.2<br>Satellite-monitor<br>Median<br>State: 12.9<br>Large urban: 13.0<br>Nonurban: 12.9 | Fuse-CMAQ<br>75th: 16.1<br>Max: 86.4<br>Satellite-monitor<br>State<br>75th: 17.4<br>99th: 37.4 | Correlation ( <i>r</i> ): 0.61 O <sub>3</sub> , 0.22<br>NO <sub>2</sub> , 0.26 CO, 0.21 SO <sub>2</sub><br>Copollutant models with: NA |
| <u>†Zemek et al. (2010)</u><br>Edmonton, Canada<br>1999–2002   | Three monitors averaged   | ED visits<br>Ear infection  | 8.5  | 75th: 10.9   | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA  |

**Table 5-10 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for respiratory infection.**

| Study   | Exposure Assessment                                 | Outcome Assessment                          | Mean Concentration<br>µg/m <sup>3</sup>                                     | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup>                         | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations  |
|---|---|---|---|---|--|
| †Kousha and Castner (2016)<br>Windsor, Canada<br>2004–2010  | Monitors in city<br>Number N                        | ED visits<br>Ear infection                  | 4.7   | NR  | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| <b>Older adults</b>   |   |   |   |   |  |
| Dominici et al. (2006)<br>204 U.S. counties<br>1999–2002    | Monitors in county averaged<br>Number per county NR | Hospital admissions<br>URI + LRI            | 13.4  | 75th: 15.2  | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| †Bell et al. (2015)<br>213 U.S. counties<br>1999–2010       | Monitors in county averaged<br>Number per county NR | Hospital admissions<br>URI + LRI            | U.S.: 12.3<br>Northeast: 12.0<br>Midwest: 12.9<br>South: 12.4<br>West: 11.3 | Max U.S.: 20.2<br>Northeast: 16.4<br>Midwest: 16.5<br>South: 16.5<br>West: 20.2 | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| Ito (2003)<br>Detroit, MI<br>1992–1994                      | One monitor<br>Sited in Windsor, Ontario            | Hospital admissions<br>Type of infection NR | 18  | 75th: 21<br>95th: 42  | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| Zanobetti and Schwartz<br>(2006)<br>Boston, MA<br>1995–1999 | One monitor<br>Data missing for 1998                | Hospital admissions<br>Pneumonia            | Median:<br>11.1   | 75th: 16.1<br>95th: 26.3  | Correlation (r): 0.20 O <sub>3</sub> , 0.55,<br>NO <sub>2</sub> , 0.52 CO<br>Copollutant models with: NA |
| †Halonen et al. (2009b)<br>Helsinki, Finland<br>1998–2004   |   | Hospital admissions<br>Pneumonia            | Median:<br>9.5  | 75th: 11.7<br>Max: 69.5   | Correlation (r) = 0.39 NO <sub>2</sub> ,<br>0.30 CO<br>Copollutant models with: NO <sub>2</sub> ,<br>CO  |
| <b>All adults</b>   |   |   |   |   |  |

**Table 5-10 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for respiratory infection.**

| Study  | Exposure Assessment      | Outcome Assessment               | Mean Concentration<br>µg/m <sup>3</sup>                              | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations  |
|--|--------------------------|----------------------------------|--|---|--|
| †Hälonen et al. (2009a)<br>Helsinki, Finland<br>1998–2004  | Two monitors             | Hospital admissions<br>Pneumonia | Median:<br>8.8   | 75th: 11.0<br>Max: 41.5                                 | Correlation (r): 0.43 O <sub>3</sub> .<br>Copollutant models with: O <sub>3</sub>  |
| †Rodopoulou et al. (2015)<br>Little Rock, AR<br>2002–2012  | One monitor              | ED visits<br>ARI and pneumonia   | 12.4   | 75th: 15.6  | Correlation (r): 0.33 O <sub>3</sub><br>Copollutant models with: O <sub>3</sub>  |
| †Liu et al. (2016)<br>Greater Houston area, TX<br>2008–2013<br>Mostly adults (92%)   | Four monitors averaged   | Hospital admissions<br>Pneumonia | 12.0   | 90th: 18.5  | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| †Belleudi et al. (2010)<br>Rome, Italy<br>2001–2005  | One monitor              | Hospital admissions<br>LRI       | 22.8   | 75th: 27.8  | Correlation (r): 0.84 PM <sub>10</sub><br>Copollutant models with: NA  |
| †Sarnat et al. (2015)<br>St. Louis, MO (eight Missouri<br>counties, eight Illinois<br>counties)<br>2001–2003<br>All adults       | One monitor              | ED visits<br>Pneumonia           | 18.0   | 75th: 22.7<br>Max: 48.7                                 | Correlation (r): 0.23 O <sub>3</sub> , 0.35<br>NO <sub>2</sub> , 0.25 CO, 0.08 SO <sub>2</sub><br>Copollutant models with: NA  |
| <b>All ages</b>  |                          |                                  |  |   |  |
| †Krall et al. (2016)<br>Atlanta, GA, 1999–2009<br>Birmingham, AL, 2004–2010<br>St. Louis, MO, 2001–2007<br>Dallas, TX, 2006–2009 | One monitor in each city | ED visits<br>URI and pneumonia   | Atlanta: 15.6<br>Birmingham: 17.0<br>St. Louis: 13.6<br>Dallas: 10.7 | NR  | Correlation (r): 0.57 O <sub>3</sub> , 0.39<br>NO <sub>2</sub> Atlanta, 0.42 O <sub>3</sub> , –0.15<br>NO <sub>2</sub> Dallas, 0.29 O <sub>3</sub> , 0.29<br>NO <sub>2</sub> St. Louis.<br>Copollutant models with: NA |

**Table 5-10 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for respiratory infection.**

| Study   | Exposure Assessment  | Outcome Assessment                                | Mean Concentration<br>µg/m <sup>3</sup>                    | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations  |
|---|--|---|--|---|--|
| Peel et al. (2005)<br>Atlanta, GA<br>1998–2000  | One monitor  | ED visits<br>URI and pneumonia                    | 19.2   | 90th: 32.3  | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| †Malig et al. (2013)<br>35 California counties,<br>2005–2008<br>†Ostro et al. (2016)<br>Eight California counties,<br>2005–2008 | Nearest monitor<br>Monitor within 25 or 20 km of<br>population-weighted zip code<br>centroid | ED visits<br>ARI and pneumonia                    | 35 counties: 5.2 to<br>19.8<br>8 counties: 16.5<br>overall | NR  | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| Stieb et al. (2009)<br>Halifax, Montreal, Toronto,<br>Ottawa, Edmonton,<br>Vancouver, Canada<br>1992–2003 across cities         | One monitor  | ED visits<br>URI + LRI                            | 6.7–9.8  | 75th<br>8.7–11.9  | Correlation (r): –0.05 to 0.62<br>O <sub>3</sub> , 0.27–0.51 NO <sub>2</sub> ,<br>0.01–0.42 CO, 0.01–0.55<br>SO <sub>2</sub> .<br>Copollutant models with: NA                        |
| Host et al. (2008)<br>Paris, Le Havre, Toulouse,<br>Rouen, Marseille, Lille,<br>France, 2000–2003                               | Seven monitors   | Hospital admissions<br>URI + LRI                  | 13.8–18.8  | 95th<br>26.3–33.0                                       | Copollutant correlation (r): NA<br>Copollutant models with: NA   |
| †Winqvist et al. (2012)<br>St. Louis, MO<br>2001–2007   | One monitor  | Hospital admissions<br>and ED visits<br>Pneumonia | 14.4   | Max: 56.6   | Correlation (r): 0.25 O <sub>3</sub><br>Copollutant models with: NA  |
| †Kim et al. (2012)<br>Denver, CO<br>2003–2007   | One monitor  | ED visits<br>Pneumonia                            | 8.0  | Max: 59.4   | Correlation (r): 0.30 O <sub>3</sub> , 0.26<br>NO <sub>2</sub> , 0.23 CO, 0.23 SO <sub>2</sub><br>Copollutant models with: NA  |
| †Cheng et al. (2015)<br>Kaohsiung, Taiwan<br>2006–2010  | Six monitors averaged  | Hospital admissions<br>Pneumonia                  | Median:<br>44.3  | 75th: 61.9<br>Max: 144                                  | Correlation (r): 0.42 O <sub>3</sub> , 0.80<br>NO <sub>2</sub> , 0.81 CO, 0.25 SO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> ,<br>NO <sub>2</sub> , CO, SO <sub>2</sub> |

**Table 5-10 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and hospital admissions and emergency department (ED) visits for respiratory infection.**

| Study   | Exposure Assessment   | Outcome Assessment                                    | Mean Concentration<br>µg/m <sup>3</sup> | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations              |
|---|-----------------------|---|---|---|--|
| †Grineski et al. (2011)<br>El Paso, TX<br>2000–2003   | Two monitors averaged | Hospital admissions<br>Acute bronchitis               | 12.8                                    | 75th: 15.6<br>95th: 26.6<br>Max: 119.1                  | Copollutant correlation ( <i>r</i> ): NA<br>Copollutant models with: NA      |
| †Winguist et al. (2012)<br>St. Louis, MO<br>2001–2007 | Two monitors averaged | Hospital admissions<br>and ED visits                  | 14.4                                    | Max: 56.6   | Correlation ( <i>r</i> ): 0.25 O <sub>3</sub><br>Copollutant models with: NA |
| †Sinclair et al. (2010)<br>Atlanta, GA<br>1998–2002   | One monitor           | Outpatient visits for<br>acute respiratory<br>illness | 17.1                                    | NR  | Copollutant correlation ( <i>r</i> ): NA<br>Copollutant models with: NA      |

ARI = acute respiratory infection, avg = average, CMAQ = community multiscale air quality, CO = carbon monoxide, ED = emergency department, IDW = inverse distance weighted, IQR = interquartile range, LRI = lower respiratory infection, max = maximum, NO<sub>2</sub> = nitrogen dioxide, NR = not reported, O<sub>3</sub> = ozone, PM<sub>2.5</sub> = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, R<sup>2</sup> = coefficient of determination, SD = standard deviation, SO<sub>2</sub> = sulfur dioxide, URI = upper respiratory infection.

†Studies published since the 2009 PM ISA.

#### 5.1.5.1.1 Hospital Admissions

Studies examined the association between short-term PM<sub>2.5</sub> exposure and hospital admissions for a variety of respiratory infections. Several recent multicounty studies conducted in the U.S. examined associations between short-term PM<sub>2.5</sub> exposure and hospital admissions for respiratory infections in children age 1 to 9 years (Yap et al., 2013) and in individuals 65 years of age and older (Bell et al., 2015). Yap et al. (2013) evaluated pediatric (children ages 1 to 9 years) hospital admissions for respiratory conditions associated with PM<sub>2.5</sub> exposures in 12 California counties. For acute respiratory infections, including pneumonia, relative risks (RR) ranged from 1.03 to 1.07 in Los Angeles, Riverside, San Bernardino, and San Diego counties at lags 0–2 days. The association for combined respiratory infection hospital admissions was significantly higher in the south coast than the central valley (RR 1.07 vs. 0.99); confidence intervals were not reported. In addition to this evidence for pediatric infections, in a multicounty time-series analysis of adults conducted in 213 U.S. counties Bell et al. (2015) reported a 0.21% (95% CI: –0.07, 0.49) increase in combined respiratory tract infection hospital admissions among adults aged 65 and older at lag 0.

In addition to the multicounty studies presented above, several single-city studies were conducted in the U.S. and internationally that examined respiratory infection hospital admissions. Grineski et al. (2011) primarily focused on examining the effect of dust and low wind events on asthma and acute bronchitis hospital admissions in El Paso, TX. The authors reported imprecise associations with PM<sub>2.5</sub> and acute bronchitis hospital admissions across both single and multiday lags with an OR = 1.01 (95% CI: 0.92, 1.12) at lag 0–3 days. By contrast, in Denver, CO, Kim et al. (2012) reported no association between PM<sub>2.5</sub> and pneumonia hospital admissions at any lag when examining a distributed lag model of 0–14 days (quantitative results not presented). Winquist et al. (2012) conducted a study in the St. Louis-MO metropolitan area to evaluate the impact of the type of health care visit on the association with short-term air pollution exposures, including PM<sub>2.5</sub>. This study compared four visit types including ED visits, hospital admissions, hospital admissions that came through the ED, and nonelective hospital admissions. The authors found that compared with ED visits patients, hospital admission patients tended to be older, had evidence of greater severity for some outcomes, and had a different mix of specific outcomes. For pneumonia, associations with PM<sub>2.5</sub> were positive only among the 2–18-year-old group for ED visits, nonelective hospital admissions, and hospital admissions through ED types of visits. The only positive association was observed for hospital admissions through ED visits (0.43% [95% CI: –0.56, 0.68] at lag 0–4 days. In Rome, Italy, Belleudi et al. (2010) reported evidence of an association between PM<sub>2.5</sub> and lower respiratory tract infection hospital admissions among adults aged 35 years and older (3.62% [95% CI: –0.96, 8.42]; lag 0–6 DL).

#### 5.1.5.1.2 Emergency Department (ED) Visits

Several recent multicity studies conducted in the U.S. examined associations between short-term PM<sub>2.5</sub> exposure and respiratory infection-related ED visits. In a multicity study conducted in 35 California counties, [Malig et al. \(2013\)](#) examined the association between short-term PM<sub>2.5</sub> exposures and ED visits, including pneumonia and acute respiratory infections. Using a time-stratified case-crossover analysis, the authors reported positive associations at 1-day lags between short-term PM<sub>2.5</sub> and acute respiratory infections (1.9% [95% CI: 1.1, 2.7]) and pneumonia (0.86% [95% CI: -0.06, 1.8]) ED visits in single pollutant models.

The evidence for associations with ED visits from single-city studies also expanded considerably since the 2009 PM ISA ([U.S. EPA, 2009](#)). [Winquist et al. \(2012\)](#) observed a positive association for hospital admissions through ED visits, can be compared to a more recent study conducted in the same St. Louis Missouri-Illinois (MO-IL) metropolitan area. However, unlike [Winquist et al. \(2012\)](#), [Sarnat et al. \(2015\)](#) found no evidence of an associations between PM<sub>2.5</sub> and pneumonia ED visits (RR = 0.98 [95% CI: 0.96, 1.00]) at lag 0–2 days.

Several studies investigated the associations between PM<sub>2.5</sub> and ED visits related to several respiratory infections in Atlanta, GA. [Darrow et al. \(2014\)](#) conducted an 18-year (1993–2010) study examining the association between PM<sub>2.5</sub> and pediatric (ages 0–4) ED visits for respiratory infections, including bronchitis and bronchiolitis, pneumonia, and upper respiratory infection (URI). Daily concentrations of ambient air pollution from several networks of ambient monitors were combined using population-weighting. Pneumonia ED visits were positively associated with PM<sub>2.5</sub> (for children aged 0–4 years, RR = 1.01 [95% CI: 0.99, 1.03]). PM<sub>2.5</sub> at lag 0–2 days was not associated with an increase in ED visits for bronchiolitis and bronchitis, although some of the point estimates in the children aged 1–4 years were positive, but uncertain for URI and pneumonia. In the same location, [Strickland et al. \(2015\)](#) examined children ages 0–18 years old between 2002–2010 in a case-crossover study using predicted daily PM<sub>2.5</sub> concentrations from a two-stage spatiotemporal model with geographical weighting. The authors found that the association with ED visits for bronchitis and upper respiratory infection increased slightly at lag 0-day (OR: 1.010 [95% CI: 0.994, 1.027], and OR: 1.015 [95% CI: 1.008, 1.022]). In contrast, the association for pneumonia-related ED visits were essentially null at both a 0-day lag (OR: 0.999 [95% CI: 0.979, 1.019]) and a 1-day lag (OR: 1.001 [95% CI: 0.981, 1.022]).

In contrast to the results of [Winquist et al. \(2012\)](#), other single-city studies such as [Darrow et al. \(2014\)](#), [Strickland et al. \(2015\)](#), and [Rodopoulou et al. \(2015\)](#) found no associations for respiratory infection ED visits. For example, in Little Rock, AR, [Rodopoulou et al. \(2015\)](#) found an association of -1.34% (95% CI: -5.31, 2.79) amongst all age groups using a 2-day lag. The association slightly increased to -0.82% after the inclusion of O<sub>3</sub> in a copollutant model (95% CI: -4.96, 3.50).

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#### 5.1.5.2 Outpatient and Physician Visit Studies

1 A study conducted in Atlanta, GA, [Sinclair et al. \(2010\)](#) examined the association between air  
2 pollution and several respiratory-related outpatient visits, including upper and lower respiratory  
3 infections. The authors separated the analysis into two consecutive time periods to compare the air  
4 pollutant concentrations and relationships for acute respiratory visits for the 25-month time-period  
5 examined in a previous study (August 1998–August 2000) and an additional 28-month time-period of  
6 available data from the Atlanta Aerosol Research and Inhalation Epidemiology Study (ARIES)  
7 (September 2000–December 2002). Across the two-time periods, 24-hour average PM<sub>2.5</sub> concentrations  
8 were lower in the 28-month versus the 25-month time-period (16.2 vs. 18.4 µg/m<sup>3</sup>, respectively). A  
9 comparison of the two-time periods indicated that associations for PM<sub>2.5</sub> tended to be larger in the earlier  
10 25-month period compared to the later 28-month period. The highest association with LRI was observed  
11 for lag 3–5 in the 25-month time-period (RR: 1.071 [95% CI: 1.003, 1.144]). For URI in the 25-month  
12 period, the association was positive at lag 0–2 days (RR: 1.015 [95% CI: 0.990, 1.040]). It should be  
13 noted that the severity of a PM<sub>2.5</sub>-related respiratory outcome, personal behavior such as delaying a visit  
14 to the doctor for less severe symptoms, and insurance type (i.e., physician visits which often are  
15 ascertained for members of a managed care organization) may dictate whether individuals visit the doctor  
16 or a hospital, making it difficult to readily compare results between studies focusing on physician visits  
17 versus hospital admissions and ED visits.

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#### 5.1.5.3 Subclinical Effects Underlying Respiratory Infection

18 Subclinical effects have been investigated solely in animal toxicological studies. As described in  
19 the 2004 PM AQCD ([U.S. EPA, 2004](#)), [Zelikoff et al. \(2003\)](#) showed that exposure to PM<sub>2.5</sub> CAPs in  
20 New York City resulted in altered macrophage function in rats. In addition, a greater bacterial burden was  
21 found when infection with *S. pneumoniae* was followed 48 hours later by PM<sub>2.5</sub> CAPs exposure.  
22 However, when PM<sub>2.5</sub> CAPs exposure preceded *S. pneumoniae* infection, it had little effect on bacterial  
23 burden. Studies described in the 2009 PM ISA ([U.S. EPA, 2009](#)) demonstrated altered susceptibility to  
24 infectious agents following exposure to whole motor vehicle exhaust and effects due to metal-enriched  
25 particles (i.e., ROFA). Recent studies of respiratory-related infection did not examine the effects of PM<sub>2.5</sub>  
26 CAPs or seek to distinguish between the effect of gaseous and particulate components in a mixture.

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#### 5.1.5.4 Summary of Respiratory Infection

27 The body of evidence for associations between short-term exposure to PM<sub>2.5</sub> and respiratory  
28 infection is comprised mainly of studies of hospital admissions and ED visits. These studies increased in  
29 number since the last review. However, because of variability in the type of respiratory infection outcome  
30 examined, the overall interpretation of findings is more complicated. Associations reported in single-city

1 studies were often imprecise, with confidence intervals crossing the null. A few recent single-city studies  
2 reported positive associations for acute bronchitis hospital admissions and respiratory tract infection  
3 hospital admissions. In several multicity studies, one conducted in the U.S. and one in or Canada,  
4 studying PM<sub>2.5</sub> and hospital admissions for respiratory infections, both reported positive associations.  
5 Most single-city studies in the U.S. consistently reported positive associations for pneumonia (adults and  
6 children, ages 0–4), but this effect was not observed for bronchiolitis and bronchitis in children ages 0–4.  
7 In contrast, a study of acute respiratory infection ED visits reported no evidence of an association with  
8 PM<sub>2.5</sub>. However, a single-city U.S. study reported positive associations with outpatient visits for lower  
9 and upper respiratory tract infections. Moreover, these studies generally provide inconsistent evidence for  
10 seasonal patterns in the strength of association. A single experimental study in animals, demonstrating  
11 altered macrophage function and increased susceptibility to pneumonia in response to PM<sub>2.5</sub> CAPs  
12 exposure, supports findings of epidemiologic studies.

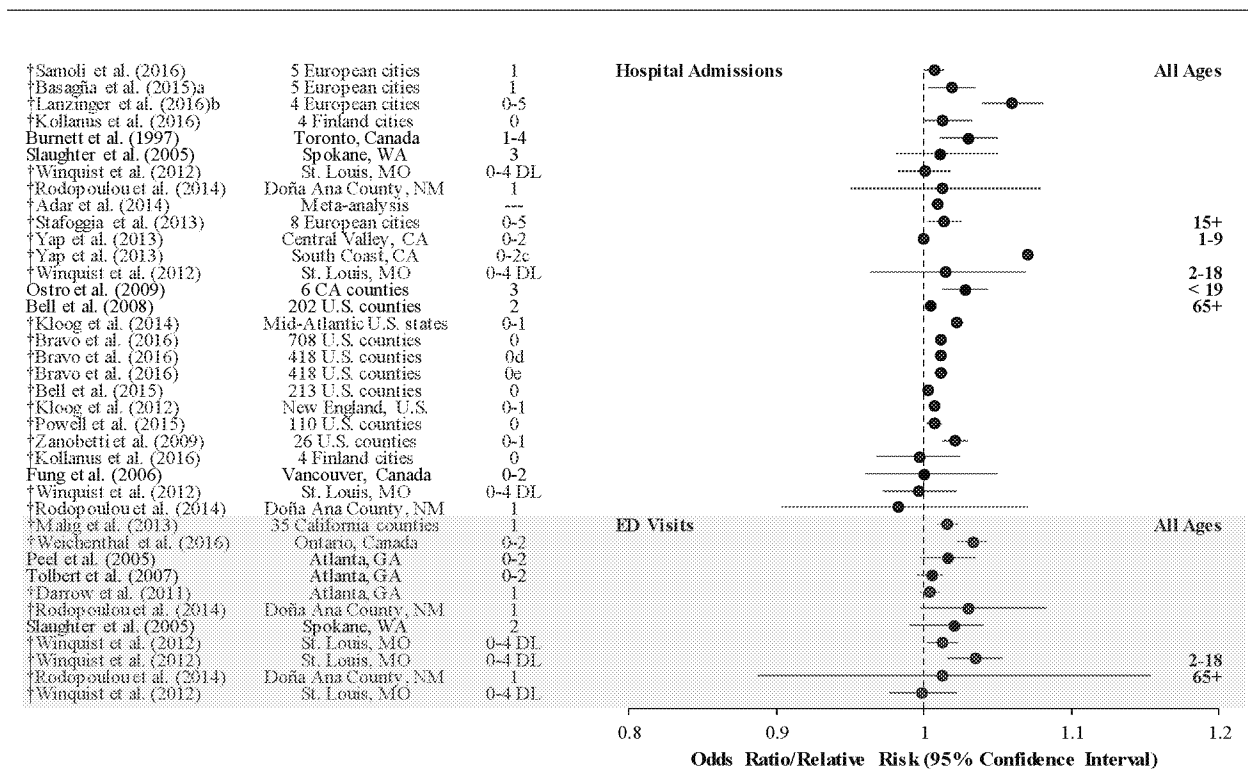
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#### 5.1.6 Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

13 In addition to individual respiratory diseases, epidemiologic studies examined respiratory  
14 diseases in aggregate where, in some cases, the aggregate represented all respiratory diseases while, in  
15 others, a specific combination of respiratory diseases was represented (e.g., COPD, asthma and  
16 respiratory infections). In the 2009 PM ISA (U.S. EPA, 2009) there was a small number of studies that  
17 examined short-term PM<sub>2.5</sub> exposure and all respiratory-related diseases in the context of hospital  
18 admissions and ED visits. These studies generally encompassed single-city studies and reported evidence  
19 of consistent, positive associations when examining effects in children, people of all ages, adults, and  
20 older adults (i.e., ≥65 years of age) at lags within the range of 0 to 2 days. However, across these studies  
21 the evaluation of potential copollutant confounding was limited to analyses of PM<sub>10–2.5</sub>, with no  
22 evaluation of gaseous pollutants. When interpreting these results, it is often difficult to determine if the  
23 associations observed indicate that PM<sub>2.5</sub> may affect the spectrum of respiratory diseases or reflects the  
24 evidence supporting associations with specific respiratory diseases, such as asthma.

25 Studies published since the completion of the 2009 PM ISA (U.S. EPA, 2009) report generally  
26 consistent, positive associations across studies of hospital admissions and ED visits for all age ranges,  
27 particularly in multicity studies (Figure 5-8). Among studies that examined both combinations of  
28 respiratory diseases grouped together and individual respiratory diseases, as detailed in previous sections  
29 within this chapter, most observed positive PM<sub>2.5</sub> associations with asthma (Section 5.1.2), respiratory  
30 infection (Section 5.1.5), or both, with results for COPD (Section 5.1.4) being more variable. However,  
31 some studies show associations with all three respiratory diseases. For studies that did not observe  
32 PM<sub>2.5</sub>-related increases in hospital admissions or ED visits for all respiratory-related diseases, associations  
33 were often observed for individual respiratory diseases within the same study, for example asthma  
34 [e.g., Yap et al. (2013)]. Similar to the individual respiratory diseases discussed earlier within this

chapter, positive associations with respiratory-related diseases are more consistently observed among children and when examining people of all ages. However, recent studies further expand analyses with older adults, with multicity studies conducted in the U.S. providing evidence of consistent, positive associations between short-term PM<sub>2.5</sub> exposure and respiratory-related diseases.



DL = distributed lag.

Note: †Studies published since the 2009 PM ISA. Black text: U.S. and Canadian studies included in the 2009 PM ISA. a = five European cities as part of the MED-PARTICLES project; b = only four of the five cities had PM<sub>2.5</sub> data; c = quantitative data for confidence intervals not reported, but above the null; d = monitoring data result; e = downscaler CMAQ, only counties and days with monitoring data. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-8 Summary of associations from studies of short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admission and emergency department (ED) visits for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

Consistent with earlier sections, the focus of this section is on those studies that address uncertainties and limitations in the evidence for association between short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admissions and ED visits identified at the completion of the 2009 PM ISA (U.S. EPA, 2009). For each of the studies that evaluated hospital admissions and ED visits for combinations of respiratory-related diseases, Table 5-11 presents the air quality characteristics of each

city, or across all cities, the exposure assignment approach used, and information on copollutants examined. Other recent studies of hospital admissions and ED visits for respiratory-related diseases that did not address uncertainties and limitations in the evidence previously identified are not the focus of this evaluation. Additionally, many of these other studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these other studies can be found in HERO: <https://hero.epa.gov/hero/particulate-matter>.

In addition to examining the relationship between short-term PM<sub>2.5</sub> exposure and respiratory effects, some epidemiologic studies often conduct analyses to assess whether the associations observed are due to chance, confounding, or other biases. As such, this evidence across epidemiologic studies is not discussed within this section, but evaluated in an integrative manner and focuses specifically on those analyses that address policy-relevant issues (Section 5.1.10), and includes evaluations of copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on PM<sub>2.5</sub> associations (Section 5.1.10.4), averaging time of PM<sub>2.5</sub> concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues and evaluated within this section consist only of epidemiologic studies that conducted time-series or case-crossover analyses focusing on combinations of respiratory-related ED visits and hospital admissions.

**Table 5-11 Epidemiologic studies of PM<sub>2.5</sub> and respiratory-related hospital admissions and emergency department (ED) visits.**

| Study, Location, Years, Age Range  | Exposure Assessment                    | ICD Codes<br>ICD-9 or ICD-10           | Mean<br>Concentration<br>µg/m <sup>3</sup> | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | Copollutant Examination   |
|--|--|--|--|---|---|
| <b>Hospital admissions</b>   |  |  |  |   |   |
| <u>Bell et al. (2008)</u><br>202 U.S. counties<br>1999–2005<br>≥65 yr                  | Average of all monitors in each county | 490–492; 464–466;<br>480–487           | NR   | NR  | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA   |
| <u>Bell et al. (2009a)</u><br>168 U.S. counties<br>1999–2005<br>≥65 yr                 | Average of all monitors in each county | 490–492; 464–466;<br>480–487           | NR   | NR  | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA   |
| <u>Ostro et al. (2009)</u><br>Six California counties<br>2000–2003<br><19 yr           | Average of all monitors in each county | 460–519                                | 19.4                                       | NR  | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA   |
| <u>Fung et al. (2006)</u><br>Vancouver, Canada<br>1995–1999<br>≥65 yr                  | Average of all monitors                | 460–519                                | 7.7  | Max: 32   | Correlation ( <i>r</i> ): –0.03 O <sub>3</sub> ,<br>0.36 NO <sub>2</sub> , 0.23 CO, 0.42<br>SO <sub>2</sub><br>Copollutant models with: NA  |
| <u>Burnett et al. (1997)</u><br>Toronto, Canada<br>1992–1994, summers only<br>All ages | One monitor                            | 464–466; 490; 480–486;<br>491–494, 496 | 16.8                                       | 75th: 23<br>95th: 40<br>Max: 66                         | Correlation ( <i>r</i> ): 0.32 O <sub>3</sub> , 0.45<br>NO <sub>2</sub> , 0.42 CO, 0.49 SO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> ,<br>CO, NO <sub>2</sub> , SO <sub>2</sub> |

**Table 5-11 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory related hospital admissions and emergency department (ED) visits.**

| Study, Location, Years, Age Range  | Exposure Assessment  | ICD Codes<br>ICD-9 or ICD-10   | Mean Concentration<br>µg/m <sup>3</sup>                                     | Upper Percentile Concentrations<br>µg/m <sup>3</sup>                            | Copollutant Examination                            |
|--|--|--------------------------------|---|---|--|
| †Powell et al. (2015)<br>119 U.S. counties<br>1999–2010<br>≥65 yr                              | Average of all monitors in each county   | 464–466, 480–487; 490–492      | 12.1 <sup>a</sup>   | 75: 14.2  | Correlation (r): NA<br>Copollutant models with: NA |
| †Bravo et al. (2017)<br>708 U.S. counties, Eastern 2/3rd of U.S.<br>2002–2006<br>≥65 yr        | Average of all monitors within a county<br>County-level population-weighted average of PM <sub>2.5</sub> concentrations predicted by downscaler CMAQ at census tract centroids<br>Same as (2), but only for counties and days with monitoring data | 464–466, 480–487; 490–492      | Monitors: 12.5<br>Downscaler CMAQ: 12.6<br>Downscaler CMAQ Subset: 12.6     | NR  | Correlation (r): NA<br>Copollutant models with: NA |
| †Bell et al. (2015)<br>213 U.S. counties<br>1999–2010<br>≥65 yr                                | Average of all monitors in each county   | 464–466, 480–487; 490–492; 493 | U.S.: 12.3<br>Northeast: 12.0<br>Midwest: 12.9<br>South: 12.4<br>West: 11.3 | Max U.S.: 20.2<br>Northeast: 16.4<br>Midwest: 16.5<br>South: 16.5<br>West: 20.2 | Correlation (r): NA<br>Copollutant models with: NA |
| †Zanobetti et al. (2009)<br>26 U.S. counties<br>2000–2003<br>≥65 yr                            | Average of all monitors in each county   | 460–519                        | 15.3  | NR  | Correlation (r): NA<br>Copollutant models with: NA |
| †Bell et al. (2014)<br>Three Connecticut and one Massachusetts counties<br>2000–2004<br>≥65 yr | One monitor in each of three counties, two averaged in one Connecticut county  | 464–466, 480–487; 490–492      | 14.0  | NR  | Correlation (r): NA<br>Copollutant models with: NA |

**Table 5-11 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory related hospital admissions and emergency department (ED) visits.**

| Study, Location, Years, Age Range  | Exposure Assessment  | ICD Codes<br>ICD-9 or ICD-10         | Mean<br>Concentration<br>µg/m <sup>3</sup> | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | Copollutant Examination  |
|--|--|--------------------------------------|--|---|--|
| †Kloog et al. (2012)<br>New England, U.S.<br>2000–2006<br>≥65 yr                                 | Predicted daily concentrations to 10 km <sup>2</sup> grid cells based on AOD observation data and 78 monitoring sites code as detailed in <a href="#">Kloog et al. (2011)</a> , R <sup>2</sup> = 0.81, then matched to zip codes | 460–519                              | 9.6  | 75th: 11.7<br>Max: 71.6                                 | Correlation (r): NA<br>Copollutant models with: NA   |
| †Kloog et al. (2014) <sup>c</sup><br>Mid-Atlantic States, U.S.<br>2000–2006<br>≥65 yr            | Predicted daily concentrations to 10-km <sup>2</sup> grid cells based on AOD observation data and 78 monitoring sites code as detailed in <a href="#">Kloog et al. (2011)</a> , R <sup>2</sup> = 0.81, then matched to zip codes | 460–519                              | 11.9                                       | 75th: 14.7<br>Max: 95.9                                 | Correlation (r): NA<br>Copollutant models with: NA   |
| †Yap et al. (2013)<br>12 counties, Central Valley and South Coast, CA<br>2000–2005<br>1–9 yr     | Average of all monitors in each county   | 460–466, 480–486; 493                | 12.8–24.6                                  | NR  | Correlation (r): NA<br>Copollutant models with: NA   |
| †Samoli et al. (2016a)<br>Five European cities<br>2001–2011<br>All ages                          | Average of all monitors in each city   | 466, 480–487; 490–492, 494, 496; 493 | 7.8–22.7                                   | NR  | Correlation (r): NA<br>Copollutant models with: NA   |
| †Lanzinger et al. (2016b) <sup>d</sup><br>Four European cities (UFIREG)<br>2011–2014<br>All ages | Average of all monitors in each city   | J00–J99                              | 14.9–20.7                                  | Max: 78.8–114.8   | Correlation (r): 0.55–0.73<br>NO <sub>2</sub> , 0.41–0.61 PM <sub>10–2.5</sub> , 0.25–0.37 UFP, 0.49–0.50 PNC<br>Copollutant models with: NA |

**Table 5-11 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory related hospital admissions and emergency department (ED) visits.**

| Study, Location, Years, Age Range   | Exposure Assessment  | ICD Codes<br>ICD-9 or ICD-10 | Mean<br>Concentration<br>µg/m <sup>3</sup> | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | Copollutant Examination  |
|---|--|------------------------------|--|---|--|
| †Basagaña et al. (2015)<br>Five European cities<br>(MED-PARTICLES)<br>2001–2010<br>All ages | One monitor in each city   | 460–519, J00–J99             | 16.0–27.6                                  | NR  | Correlation ( <i>r</i> ): NR<br>Copollutant models with: NR  |
| †Stafoggia et al. (2013)<br>Eight European cities<br>(MED-PARTICLES)<br>2003–2013<br>≥15 yr | Average of all monitors in each city   | 460–519                      | 17.2–34.4                                  | NR  | Correlation ( <i>r</i> ): >0.60 with NO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> , NO <sub>2</sub> , PM <sub>10–2.5</sub> |
| †Jones et al. (2015)<br>New York State<br>2000–2005<br>All ages                             | Fused-CMAQ <sup>b</sup> to 12-km <sup>2</sup> grid cells, geocoded addresses to each grid cell | 491, 492, 493, 496           | 8.0  | 75th: 11.1<br>Max: 69.5                                 | Correlation ( <i>r</i> ): –0.34–0.59 O <sub>3</sub><br>Copollutant models with: NA   |
| †Kim et al. (2012)<br>Denver, CO<br>2003–2007<br>All ages                                   | One monitor  | 480–486; 490–493, 496        | 7.9  | Max: 59.4   | Correlation ( <i>r</i> ): 0.68 SO <sub>4</sub> <sup>2–</sup> , 0.82 NO <sub>3</sub> <sup>–</sup><br>Copollutant models with: NA          |
| †Kollanus et al. (2016)<br>Helsinki, Finland<br>2001–2010<br>All ages                       | One urban background monitor and one regional background monitor                               | J00–J99                      | 8.6  | 75th: 10.8<br>Max: 54.1                                 | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA  |

**Table 5-11 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory related hospital admissions and emergency department (ED) visits.**

| Study, Location, Years, Age Range  | Exposure Assessment  | ICD Codes<br>ICD-9 or ICD-10   | Mean<br>Concentration<br>µg/m <sup>3</sup>                                 | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup>   | Copollutant Examination  |
|--|--|--|--|---|--|
| <b>ED visits</b>   |  |  |  |   |  |
| <u>Peel et al. (2005)</u><br>Atlanta, GA<br>1993–2000<br>All ages              | One monitor  | 460–466, 477; 480–486;<br>491, 492, 496; 493, 786.09   | 19.2   | 90th: 32.3  | Correlation ( <i>r</i> ): 0.55–0.68,<br>CO, NO <sub>2</sub><br>Copollutant models with: NA   |
| <u>Tolbert et al. (2007)</u><br>Atlanta, GA<br>1993–2004<br>All ages           | One monitor  | 460–465, 460.0, 477;<br>480–486; 491, 492, 496;<br>493, 786.07, 786.09;<br>466.1, 466.11, 466.19 | 17.1   | 75th: 21.9<br>90th: 28.8<br>Max: 65.8   | Correlation ( <i>r</i> ): 0.62 O <sub>3</sub> , 0.47<br>NO <sub>2</sub> , 0.47 CO, 0.17 SO <sub>2</sub> ,<br>0.47 PM <sub>10–2.5</sub><br>Copollutant models with: NA  |
| <u>†Malig et al. (2013)</u><br>35 California counties<br>2005–2008<br>All ages | Nearest monitor within 20 km<br>from population-weighted<br>centroid of each patient's<br>residential zip code | 460–519  | 5.2–19.8   | NR  | Correlation ( <i>r</i> ): NA<br>Copollutant models with:<br>PM <sub>10–2.5</sub>   |
| <u>†Krall et al. (2016)</u><br>Four U.S. cities<br>1999–2010                   | One monitor in each city   | 460–465, 466.0, 477;<br>480–486; 491–493, 496,<br>786.07   | Atlanta: 15.6<br>St. Louis: 13.6<br>Dallas: 10.7<br>Birmingham: 17.0       | NR  | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA  |
| <u>†Darrow et al. (2011)</u><br>Atlanta, GA<br>1998–2004<br>All ages           | One monitor<br>24-h avg, 1-h max, commute<br>(7–10 a.m.), daytime<br>(8 a.m.–7 p.m.), nighttime<br>(12–7 a.m.) | 460–466, 477; 480–486;<br>491–493, 496, 786.09   | 24-h avg: 16<br>1-h max: 29<br>Commute: 17<br>Daytime: 15<br>Nighttime: 17 | 75th, Max:<br>24-h avg: 21, 72<br>1-h max: 36, 188<br>Commute: 21, 76<br>Daytime: 19, 71<br>Nighttime: 14, 88 | Correlation ( <i>r</i> ): 24-h avg:<br>0.46 O <sub>3</sub> , 0.52 NO <sub>2</sub> , 0.45 CO.<br>Similar for 1-h max, higher<br>for nighttime, lower for<br>daytime and commute.<br>Copollutant models with: NA |

**Table 5-11 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory related hospital admissions and emergency department (ED) visits.**

| Study, Location, Years, Age Range  | Exposure Assessment   | ICD Codes<br>ICD-9 or ICD-10   | Mean<br>Concentration<br>µg/m <sup>3</sup> | Upper Percentile<br>Concentrations<br>µg/m <sup>3</sup> | Copollutant Examination  |
|--|---|--|--|---|--|
| †Weichenthal et al. (2016)<br>Ontario, Canada (15 cities)<br>2004–2011<br>All ages | Nearest monitor to<br>population-weighted zip code<br>centroid or single available<br>monitor | J00–J99  | 7.1  | Max: 56.8   | Correlation (r): <0.42 NO <sub>2</sub><br>Copollutant models with: O <sub>3</sub> ,<br>NO <sub>2</sub> , oxidative potential |
| <b>Hospital admissions and ED visits, separately</b>                               |   |  |  |   |  |
| Slaughter et al. (2005)<br>Spokane, WA<br>1995–1999<br>All ages                    | One monitor   | 464–466, 490; 480–487;<br>491–494, 496   | NR   | 90: 20.2  | Correlation (r): 0.62 CO;<br>0.31 PM <sub>10–2.5</sub><br>Copollutant models with: NA  |
| †Winqvist et al. (2012)<br>St. Louis, MO<br>2001–2007<br>All ages                  | One monitor   | 460–465, 466.0, 466.1,<br>466.11, 466.19, 477,<br>480–486, 491–493, 496,<br>786.07 | 14.4                                       | 75th: 22.7<br>Max: 48.7                                 | Correlation (r): 0.25 O <sub>3</sub><br>Copollutant models with: NA  |
| †Rodopoulou et al. (2014)<br>Doña Ana County, NM<br>2007–2010<br>≥18 yr            | Three monitors  | 460–465, 466, 480–486,<br>490–493, 496   | 10.9                                       | 75th: 13<br>Max: 55.6                                   | Correlation (r): –0.05 O <sub>3</sub><br>Copollutant models with: NA   |

CMAQ = Community Multi-Scale Air Quality model; MED-PARTICLES = particles size and composition in Mediterranean countries; Geographical variability and short-term health effects; UFIREF = Ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy.

<sup>a</sup>Median concentration.

<sup>b</sup>CMAQ predictions bias corrected using monitored data.

<sup>c</sup>PM<sub>2.5</sub> concentrations are for lag 0–1 day.

<sup>d</sup>Only four of the five cities had PM<sub>2.5</sub> data.

†Studies published since the 2009 PM ISA.

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### 5.1.6.1 Hospital Admissions

Recent studies that examined the association between short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admissions build upon the evidence detailed in the 2009 PM ISA (U.S. EPA, 2009), particularly the examination of effects in older adults (i.e., ≥65 years of age). Multicity studies conducted in Europe (Lanzinger et al., 2016b; Samoli et al., 2016a; Basagaña et al., 2015) and Finland (Kollanus et al., 2016) that examined people of all ages provide evidence of consistent, positive associations that are similar in magnitude to those reported in the U.S. and Canadian studies evaluated in the 2009 ISA (Figure 5-8). The results from analyses of people of all ages are further supported by Stafoggia et al. (2013) in a study of eight southern European cities that reported a 1.36% (95% CI: 0.23, 2.49) increase in hospital admissions at lag 0–5 days, as well as a meta-analysis conducted by Adar et al. (2014) (RR = 1.01 [95% CI: 1.00, 1.02]). However, single-city studies conducted in St. Louis, MO (Winquist et al., 2012) and Doña Ana County, NM (Rodopoulou et al., 2014), do not provide consistent evidence of an association with respiratory-related diseases in all ages analyses.

Studies that examined the relationship between short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admissions in children are limited in number, but generally report associations that are similar in magnitude to previous studies. An exception is the study conducted by Yap et al. (2013) in 12 California counties focusing on children 1 to 9 years of age where there was no evidence of an association in the central valley counties (RR = 1.0), but a positive association in the south coast counties was seen (RR = 1.07) at lag 0–2 days. Winquist et al. (2012) also reported a positive association for children in St. Louis, MO, but confidence intervals were wide (RR = 1.02 [95% CI: 0.96, 1.07]; lag 0–4 DL).

Most of the recent studies focusing on respiratory-related hospital admissions focus on older adults, and consisted mostly of multicounty or entire state analysis conducted in the U.S. These recent multicounty studies report evidence of consistent, positive associations, except the study by Kollanus et al. (2016) in four cities in Finland (Figure 5-8). The associations reported across the U.S. for multicounty studies are based on a variety of exposure assignment approaches (see Table 5-11), all of which resulted in associations that are similar in magnitude. In a multicounty time-series analysis conducted in 213 U.S. counties from 1999–2010, Bell et al. (2015) observed a 0.25% (95% CI: 0.01, 0.48) increase in all respiratory hospital admissions at lag 0 among adults aged 65 years and older. In a similar study of 110 U.S. counties, Powell et al. (2015) reported results consistent with Bell et al. (2015) (0.67% [95% CI: 0.14, 1.2]; lag 0). Bell et al. (2014), also examined single-day lags, but in four counties in Connecticut and Massachusetts, and reported evidence of positive associations across lags of 0 to 2 days, albeit with wide confidence intervals (quantitative results not presented). Additional evidence of a positive association between short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admissions is provided by Zanobetti et al. (2009) in an analysis of 26 U.S. counties where a 2.1% (95% CI: 1.2, 3.0) increase in hospital admissions was reported at lag 0–1. The results from the epidemiologic studies that rely on

community-based monitors are supported by a series of studies that used a combination of monitored, modeled, and in some cases satellite-based PM<sub>2.5</sub> concentrations. In a multicity study conducted in the New England region of the U.S., [Kloog et al. \(2012\)](#) assessed exposure using a novel prediction model that combined land use regression with surface PM<sub>2.5</sub> measurements from satellite aerosol optical depth. The authors observed a 0.70% (95% CI: 0.35, 1.05) increase in respiratory-related hospital admissions for a 0–1-day lag. In a sensitivity analysis using monitor-based exposure assessment in the time-series analysis, [Kloog et al. \(2012\)](#) reported similar results (1.51% [95% CI: 0.42, 1.65]), but with slightly larger confidence intervals. [Kloog et al. \(2014\)](#) built upon the exposure assessment used in [Kloog et al. \(2012\)](#) in a study conducted in the Mid-Atlantic region of the U.S. The authors reported a 2.2% (95% CI: 1.9, 2.6) increase in respiratory-related hospital admissions at lag 0–1 day. The results of [Kloog et al. \(2012\)](#) and [Kloog et al. \(2014\)](#) are supported by [Bravo et al. \(2017\)](#) in a study of 708 U.S. counties. The authors examined associations between short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admissions using three different exposure assessment approaches: (1) a population-weighted average of PM<sub>2.5</sub> concentration computed in 708 U.S. counties using a downscaled CMAQ model (Section 3.3.2.4.3); (2) a population-weighted average of downscaled CMAQ-simulated PM<sub>2.5</sub> concentrations computed in the 418 U.S. counties that have monitoring data; and (3) PM<sub>2.5</sub> concentrations from the 418 U.S. counties with fixed-site monitors. Across these three exposure assignment approaches, the authors reported a relatively consistent percent increase in hospital admissions at lag 0: (1) 1.16% (95% CI: 0.88, 1.45); (2) 1.11 (95% CI: 0.66, 1.56); and (3) 1.10% (95% CI: 0.70, 1.50).

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#### 5.1.6.2 Emergency Department (ED) Visits

Compared to studies that examined hospital admissions for respiratory-related diseases, fewer studies focused on ED visits, with the majority examining associations with short-term PM<sub>2.5</sub> exposure in analyses of all ages. Additionally, a recent study examined associations with PM size fractions smaller than 2.5 µm, but larger than UFP (i.e., number concentration [NC] and surface area concentration [SC] for particles 100–300 nm), which also supports the positive associations with respiratory-related ED visits observed for PM<sub>2.5</sub> ([Leitte et al., 2011](#)). Whereas, many hospital admission studies were conducted over multiple cities or entire states, the ED visit studies are mostly limited to individual cities.

[Malig et al. \(2013\)](#), in a study of 35 California counties, reported a 1.6% (95% CI: 0.98, 2.27) increase in respiratory-related ED visits at lag 1. Building on the previous studies conducted in Atlanta, GA ([Tolbert et al., 2007](#); [Peel et al., 2005](#)), [Darrow et al. \(2011\)](#) also examined associations between short-term PM<sub>2.5</sub> exposures and respiratory-related ED visits, reporting an association similar in magnitude to the previous studies (0.4% [95% CI: –0.2, 1.0]; lag 1). Additionally, [Krall et al. \(2016\)](#) in a study of four U.S. cities (i.e., Atlanta, Birmingham, St. Louis, and Dallas) reported positive associations for each city at lag 0 (quantitative results not presented). Single-city studies conducted in Canada and the U.S. report associations that overall are consistently positive and generally similar in magnitude to [Malig et al. \(2013\)](#) (Figure 5-8). Across the studies evaluated, only [Winqvist et al. \(2012\)](#) examined associations

with respiratory related ED visits in children (i.e., 2–18 years of age) in St. Louis, MO, and reported an association larger in magnitude (RR = 1.03 [95% CI: 1.02, 1.05]; lag 0–4 DL) compared to that observed when examining people of all ages (RR = 1.01 [95% CI: 1.0, 1.02]; lag 0–4 DL). Of the few studies that examined effects in older adults (Rodopoulou et al., 2014; Winkvist et al., 2012), there was no evidence of an association between short-term PM<sub>2.5</sub> exposure and respiratory-related ED visits.

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### 5.1.6.3 Summary of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

Recent epidemiologic studies that examined short-term PM<sub>2.5</sub> exposure and hospital admissions and ED visits for respiratory-related diseases generally support the results from studies evaluated in the 2009 PM ISA (U.S. EPA, 2009). Across studies, there is evidence of generally consistent, positive associations among children, with a growing body of evidence, primarily from multicity U.S.-based studies of older adults (Figure 5-8). Additional studies focusing on people of all ages, also provide evidence supporting an association with PM<sub>2.5</sub>, with most of the studies conducted in individual cities.

The main results of studies detailed within this section are supported by analyses that examined specific policy-relevant issues as detailed in Section 5.1.10. Compared to the 2009 PM ISA (U.S. EPA, 2009), recent studies provide a more extensive examination of potential copollutant confounding, but overall the assessment is limited to only a few studies. These studies demonstrate that associations between short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admissions and ED visits are relatively unchanged in models with gaseous pollutants and PM<sub>10–2.5</sub> (Section 5.1.10.1). In addition to copollutant confounding, several studies examined the influence of alternative model specifications on the PM<sub>2.5</sub> association with respiratory-related hospital admissions and ED visits and found that associations remained relatively unchanged when accounting for temporal trends and weather covariates using different specifications (Section 0). Analyses that focused on whether there are differences by season provide some evidence that PM<sub>2.5</sub> associations are larger in magnitude during the warmer months, but some studies reported larger associations during the colder months (Section 5.1.10.4.1). The difference in associations by season could reflect geographic variability that continues to be observed in multicity studies. However, to date it remains unclear what factors contribute to the observed geographic variability in PM<sub>2.5</sub> associations with respiratory-related diseases (Bell et al., 2009a).

While studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) tended to support PM<sub>2.5</sub> associations within the first few days after exposure (i.e., lag 0 to 3 days), recent studies support that evidence and provide initial evidence indicating that PM<sub>2.5</sub> effects may be more prolonged, ranging from 0–5 days (Section 5.1.10.3). To date, there are very few studies that have examined subdaily averaging times of PM<sub>2.5</sub> concentrations (Section 5.1.10.5). In terms of respiratory-related hospital admissions and ED visits, available evidence indicates that subdaily averaging times do not result in stronger associations with respiratory-related hospital admissions and ED visits compared to a 24-hour averaging time (Section 5.1.10.5). Lastly, recent evaluations of the C-R relationship between short-term PM<sub>2.5</sub> exposure

1 and respiratory-related hospital admissions and ED visits provides evidence of a log-linear relationship,  
2 but this assessment is based on rather limited analyses that did not empirically evaluate alternatives to  
3 linearity (Section 5.1.10.6).

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### 5.1.7 Respiratory Effects in Healthy Populations

4 The 2009 PM ISA (U.S. EPA, 2009) did not have a delineated discussion of respiratory effects in  
5 healthy populations, but relevant epidemiologic studies provided inconsistent evidence for PM<sub>2.5</sub>-related  
6 decreases in lung function and increases in pulmonary inflammation, and no evidence for increases in  
7 respiratory symptoms in individuals with no underlying respiratory disease. Controlled human exposure  
8 studies evaluated in the 2009 PM ISA provided no evidence for changes in lung function and limited  
9 evidence for pulmonary inflammation, while animal toxicological studies more consistently provided  
10 evidence for PM<sub>2.5</sub> exposure-related effects.

11 To characterize the current state of the evidence, this section focuses on results specific to healthy  
12 populations. Some studies employed scripted exposures in an attempt to further inform the relationship  
13 between short-term PM<sub>2.5</sub> exposure and respiratory effects. Scripted studies measuring personal ambient  
14 PM<sub>2.5</sub> exposures are designed to minimize uncertainty in the PM<sub>2.5</sub> exposure metric by always measuring  
15 PM<sub>2.5</sub> at the site of exposure, ensuring exposure to sources of PM<sub>2.5</sub> and measuring outcomes at  
16 well-defined lags after exposure.

17 There are recent epidemiologic studies in populations with 13–28% prevalence of asthma,  
18 COPD, or atopy, some of which indicate PM<sub>2.5</sub>-associated increases in respiratory effects. However, these  
19 studies are not evaluated in this section, as it is not known whether the results apply to the healthy portion  
20 of the population or are instead driven solely by an association in individuals with pre-existing respiratory  
21 conditions, these studies can be found in HERO (<https://hero.epa.gov/hero/particulate-matter>). Further,  
22 these studies do not provide additional insight on issues such as copollutant confounding, effects at low  
23 PM<sub>2.5</sub> exposure concentrations, or critical exposure periods.

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#### 5.1.7.1 Epidemiologic Studies

24 The 2009 PM ISA (U.S. EPA, 2009) evaluated a limited number of epidemiologic studies that  
25 examined respiratory effects in healthy populations. A study of adult school crossing guards in New  
26 Jersey observed decreases in lung function associated with 1-hour max PM<sub>2.5</sub> concentrations (Fan et al.,  
27 2008). In contrast, Holguin et al. (2007) did not observe an association between PM<sub>2.5</sub> and lung function  
28 or lung inflammation in a study of school children in Ciudad Juarez, Mexico. Several recent studies are  
29 available for evaluation, with most focusing on lung function changes and/or lung inflammation in  
30 healthy populations. Study-specific details, including cohort descriptions and air quality characteristics  
31 are highlighted in Table 5-2.

## Respiratory Symptoms

While respiratory symptoms are frequently studied in populations with pre-existing respiratory conditions, such as asthma or COPD, the outcome is less often examined in healthy populations. As such, only a single recent study is available for review. In a study of school children in Santiago, Chile, 7-day average PM<sub>2.5</sub> was associated with increased odds of cough and a composite index of respiratory symptoms (Prieto-Parra et al., 2017). The associations were relatively unchanged in two-pollutant models with PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, or O<sub>3</sub>. However, copollutant correlations were not reported, limiting the interpretability of the copollutant models.

## Lung Function Changes

The majority of recent studies on lung function changes in relation to PM<sub>2.5</sub> concentrations examined adults during scripted exposures and exposure interventions. Studies examining lung function changes in adults after commuting in cars, buses, or on bicycles, did not observe associations between personal ambient PM<sub>2.5</sub> exposure and FEV<sub>1</sub> (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b). In a study of adults commuting 2 hours through Atlanta traffic, Mirabelli et al. (2015) reported PM<sub>2.5</sub>-related decreases in FVC immediately after the commute. The association appeared to be transient, with no association observed 3 hours post-commute.

A number of studies in the U.S. (Mirowsky et al., 2015), Canada (Dales et al., 2013), and Europe (Matt et al., 2016; Kubesch et al., 2015; Steenhof et al., 2013; Strak et al., 2012) used quasi-experimental designs to assign participants to either rest or exercise in different locations with notable pollutant contrasts. Similar to the studies of scripted commutes through traffic, many of these quasi-experimental studies observed null associations between lung function and PM<sub>2.5</sub> (Kubesch et al., 2015; Mirowsky et al., 2015; Strak et al., 2012). In contrast, Dales et al. (2013) observed decreases in FEV<sub>1</sub> and FEF<sub>25–75%</sub> associated with 8-hour average PM<sub>2.5</sub> concentrations in Sault Ste. Marie, Canada. Associations were observed despite low mean concentrations of 8-hour average PM<sub>2.5</sub>. Additionally, in Barcelona, Spain, Matt et al. (2016) reported that healthy adults experienced decreased FEV<sub>1</sub> associated with 2-hour average PM<sub>2.5</sub> immediately after exposure. Notably, PM<sub>2.5</sub> was associated with increased FEV<sub>1</sub> 7 hours after exposure, again indicating potentially transient effects. Another study in China implemented an exposure intervention by moving healthy, nonsmoking adults from an industrial town to a less polluted city for 9 days (Hong et al., 2010). Participants experienced increased FEV<sub>1</sub> and PEF associated with decreased 24-hour average PM<sub>2.5</sub>.

Studies of lung function in healthy children were limited in number. School-children in an agricultural area of Brazil experienced decreases in PEF in association with PM<sub>2.5</sub> concentrations measured outside of school, averaged over the 6, 12, or 24 hours preceding spirometry (Jacobson et al., 2012). In Seoul, South Korea Hong et al. (2010), composite monitor 24-hour average PM<sub>2.5</sub> was associated with a small, imprecise decrease in PEF in schoolchildren at lags 0 and 3, but no other lags

up to 4 days. The location of the monitors relative to the school was not specified, so it is not clear to what degree exposure measurement error might have impacted the results (Section 3.4.2.2).

### Subclinical Effects

Most recent studies of subclinical respiratory effects in healthy populations examined exhaled nitric oxide (eNO) as an indicator of pulmonary inflammation. Many of the same studies that were evaluated in the previous subsection on lung function also measured eNO. As such, the majority of recent studies similarly examined adults during scripted exposures. Studies of adults during and after commuting in cars, buses, or on bicycles, generally observed associations between personal ambient PM<sub>2.5</sub> exposure and subclinical respiratory effects (Mirabelli et al., 2015; Weichenthal et al., 2011; Zuurbier et al., 2011b). Mirabelli et al. (2015) observed associations between eNO and PM<sub>2.5</sub> concentrations during a 2-hour scripted commute through Atlanta traffic. The authors reported PM<sub>2.5</sub>-related increases in eNO levels 0, 1, 2, and 3 hours post-commute. A similar PM<sub>2.5</sub>-related increase in eNO was reported in a group of adults cycling alongside high- and low-traffic roads in Ottawa, Canada (Weichenthal et al., 2011). The observed associations with personal PM<sub>2.5</sub> concentrations were strongest 2 hours after cycling. Conversely, PM<sub>2.5</sub> was associated with a decrease in eNO in a study of adults commuting 2 hours by either car, bus, or bike in the Netherlands (Zuurbier et al., 2011b). However, the authors also noted that personal ambient PM<sub>2.5</sub> was associated with a decrease in Clara cell secretory protein (CC16), a pulmonary biomarker that is often decreased in subjects with lung epithelial damage.

Studies utilizing quasi-experimental designs were less consistent, despite similarly high mean concentrations of PM<sub>2.5</sub>. In New York, PM<sub>2.5</sub> exposure while walking near high-traffic roads and in a forest was associated with eNO 24 hours after exposure (Mirowsky et al., 2015). However, eNO was not associated with PM<sub>2.5</sub> in studies where participants were randomized to exercise or rest at locations with air pollution exposure contrasts in Barcelona, Spain (Kubesch et al., 2015) or Utrecht, The Netherlands (Strak et al., 2012). As part of the same project in the Netherlands, Steenhof et al. (2013) reported an association between PM<sub>2.5</sub> exposure and nasal lavage levels of the pro-inflammatory cytokine, IL-6. The observed association was persistent in two-pollutant models including NO<sub>x</sub>, O<sub>3</sub>, or SO<sub>2</sub> (Steenhof et al., 2013).

A single study examined subclinical effects in school children. Carlsen et al. (2016) observed a 5.4 ppb (95% CI: -3.1, 13.0 ppb) increase in eNO associated with 2-day average PM<sub>2.5</sub> at two schools in Umea, Sweden. PM<sub>2.5</sub> was measured at monitors located within 1.5 km of the two schools. Although copollutant models were not examined, PM<sub>2.5</sub> was weakly correlated with NO<sub>x</sub> and only moderately correlated with O<sub>3</sub>.

**Table 5-12 Epidemiologic studies of PM<sub>2.5</sub> and respiratory effects in healthy populations.**

| Study   | Study Population   | Exposure Assessment<br>Concentration in µg/m <sup>3</sup>  | Single-Pollutant Association<br>95% CI  | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations   |
|---|--|--|---|---|
| <b>Exposure interventions</b>   |  |  |   |   |
| †Hao et al. (2017)<br>Shanghai and Shandong, China<br>2012                                | N = 42, ages 50–61 yr<br>9-day relocation from higher to lower air pollution city<br>Outcomes every other day                            | Total personal<br>24-h avg<br>Mean (SD)<br>Shanghai: 95.1<br>Shandong: 187                               | Per 10 µg/m <sup>3</sup> decrease<br>FEV <sub>1</sub> : 9.0 (3.6, 14.4) mL<br>PEF: 33.2 (4.8, 61.5) mL/sec              | Correlation (r): NA<br>Copollutant models with:<br>NO <sub>2</sub>  |
| <b>Scripted outdoor exposures</b>   |  |  |   |   |
| †Mirabelli et al. (2015)<br>Atlanta, GA<br>2009–2011                                      | N = 21, ages NR<br>Morning commute on highway<br>Two times each, 75 observations<br>Outcomes 0, 1, 2, 3 h after                          | Personal in-vehicle<br>2-h avg (7–9 a.m.)<br>Mean: 28.8  | Per 20.9 µg/m <sup>3</sup><br>eNO, 0 h: 2.4% (–3.3, 8.5)<br>FEV <sub>1</sub> percent predicted, 0 h: –0.42% (–2.2, 1.3) | Correlation (r): NA<br>Copollutant models with: NA  |
| †Mirowsky et al. (2015)<br>New York, Sterling Forest NY; Nutley, NJ<br>Jun–Sep, 2011–2012 | N = 26, ages 18–33 yr<br>Walking on highway bridge, no-truck highway, forest<br>One time each, 70 observations<br>Outcomes 0, 24 h after | Personal ambient<br>2-h avg<br>Mean, max<br>Bridge: 31, 45<br>No-truck highway: 21, 50<br>Forest: 13, 24 | Increment NR<br>eNO, 0 h: –0.38% (–1.6, 0.31)<br>eNO, 24 h: 0.87% (–0.09, 1.8)  | Correlation (r): 0.66 PM <sub>10</sub> , 0.29 EC, 0.38 BC, 0.4 OC, 0.39 O <sub>3</sub><br>Copollutant models with: NA |
| †Dales et al. (2013)<br>Sault Ste Marie, Canada<br>May–Aug 2010                           | N = 61, mean (SD) age 24 (6) yr<br>Near steel plant, college campus<br>five times each<br>Outcomes 0 h after                             | Personal ambient<br>8-h avg<br>Mean (SD)<br>Steel plant: 12.8<br>College campus: 11.6                    | Per 9 µg/m <sup>3</sup><br>FEV <sub>1</sub> : –0.42% (–0.83, 0)<br>FEF <sub>25–75%</sub> : –0.92% (–1.7, –0.12)         | Correlation (r): NA<br>Copollutant models with: NA  |

**Table 5-12 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory effects in healthy populations.**

| Study   | Study Population   | Exposure Assessment<br>Concentration in µg/m <sup>3</sup>   | Single-Pollutant Association<br>95% CI   | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations  |
|---|--|---|--|--|
| †Weichenthal et al. (2011)<br>Ottawa, Canada<br>May–Sep 2010  | N = 42, ages 19–58 yr<br>Cycling on high- and low-traffic road<br>One time each, 118 observations<br>Outcomes 0, 1, 2, 3 h after   | Personal ambient<br>1-h avg<br>Mean, max<br>High-traffic road: 12.2, 34<br>Low-traffic road: 8.1, 26  | Per 8.7 µg/m <sup>3</sup><br>1-h post-exposure<br>FEV <sub>1</sub> : –16 (–90, 58) ml<br>2-h post-exposure<br>eNO: 1.1 (0.08, 2.2) ppb   | Correlation (r): (high traffic, low traffic) 0.06, –0.22 UFP; 0.32, 0.24 BC; 0.75, 0.59 CO; –0.30, –0.04 SO <sub>2</sub> ; 0.31, 0.45 NO <sub>2</sub> ; 0.58, 0.36 O <sub>3</sub><br>Copollutant models with: NA |
| †Strak et al. (2012);<br>†Steenhof et al. (2013)<br>Utrecht, the Netherlands<br>Mar–Oct 2009          | N = 31, ages 19–26 yr<br>Free-flowing traffic road, stop-and-go traffic road, urban site, farm, underground train station<br>One time each, with exercise<br>Outcomes 0, 2, 22 h after | Personal ambient<br>5-h avg<br>Geometric mean, max<br>39, 167   | Per 11.5 µg/m <sup>3</sup><br>FVC: 0.08%, <i>p</i> > 0.10<br>eNO: 0.17%, <i>p</i> > 0.10<br>For outdoor sites only<br>Nasal lavage IL-6: 16%, <i>p</i> < 0.05  | Correlation (r): –0.65 O <sub>3</sub> , 0.21 NO <sub>2</sub> , 0.31 NO <sub>x</sub><br>Copollutant models with: O <sub>3</sub> , SO <sub>2</sub> , NO <sub>x</sub>   |
| †Zuurbier et al. (2011b);<br>†Zuurbier et al. (2011a)<br>Arnhem, the Netherlands<br>Jun 2007–Jun 2008 | N = 34, ages 23–55 yr<br>Commute in car, bus, bike<br>One time each, 352 observations<br>Outcomes 0, 6 h after   | Personal ambient<br>2-h avg<br>Mean, max<br>Diesel bus: 39.1, 324<br>Diesel car: 58.1, 358<br>Gas car: 68.1, 403<br>Bike, high traffic: 49.8, 219<br>Bike, low traffic: 65.2, 241 | Per 68.1 µg/m <sup>3</sup> , 6 h post-exposure<br>FEV <sub>1</sub> : 0.02% (–0.41, 0.45)<br>MMEF: 0.60% (–0.73, 1.9)<br>eNO: –2.5% (–5.9, 1.1)<br>CC16: –1.3% (–6.8, 0.3)  | Correlation (r): NA<br>Copollutant models with: NO <sub>2</sub>  |
| †Matt et al. (2016)<br>Nov 2013–Mar 2014  | N = 30, ages 19–57 yr<br>Bridge over high-traffic road, seaside park<br>One time each, with exercise and rest<br>Outcomes 0, 7 h after   | Personal ambient<br>2-h avg<br>Mean, 95th<br>High-traffic: 82, 92<br>Seaside Park: 39, 48   | Per 1 µg/m <sup>3</sup> , 0-h post-exposure<br>FEV <sub>1</sub> : –0.55 (–1.4, 0.31) mL<br>PEF: –0.06 (–0.32, 0.21) L/min<br>Per 1 µg/m <sup>3</sup> , 7-h post-exposure<br>FEV <sub>1</sub> : 0.43 (–0.52, 1.4) mL<br>PEF: 0.15 (–0.05, 0.35) L/min | Correlation (r): –0.04 high-traffic, 0.7 seaside park NO <sub>x</sub><br>Copollutant models with: NA   |

**Table 5-12 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory effects in healthy populations.**

| Study   | Study Population   | Exposure Assessment<br>Concentration in µg/m <sup>3</sup>   | Single-Pollutant Association<br>95% CI  | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations   |
|---|--|---|---|---|
| †Kubesch et al. (2015)<br>Barcelona, Spain<br>Feb–Nov 2011              | N = 28, ages 18–60 yr<br>Bridge over high-traffic road,<br>marketplace<br>One time each, with exercise and<br>rest<br>Outcomes 0, 3, 6 h after | Personal ambient<br>2-h avg<br>Mean, 95th<br>High-traffic: 80.8, 88.6<br>Marketplace: 30.0, 37.7                        | Per IQR (NR)<br>FEV <sub>1</sub> : 0.00 (–0.02, 0.02) mL<br>FEF <sub>25–75%</sub> : –0.05 (–0.11, 0) mL<br>eNO: 0.40 (–0.53, 1.3) ppb       | Correlation (r): 0.91 NO <sub>x</sub><br>Copollutant models with: NA  |
| Fan et al. (2008)<br>Patterson, NJ<br>Feb–May 2005                      | N = 11, mean (SD) age 61 (14) yr<br>Crossing guards at work<br>Three work shifts, 27 observations<br>Outcomes 0 h after                        | Personal ambient<br>Mean (SD), max difference<br>from 24-h avg<br>1-h avg: 35.2, 87<br>1-h max: 71.3, 278               | Increment NR<br>FEV <sub>1</sub> , 1-h avg: 20 (–58, 98) mL<br>FEV <sub>1</sub> , 1-h max: –130 (–287, 27) mL                               | Correlation (r): NA<br>Copollutant models with: NA  |
| <b>General community exposures</b>                                      |  |   |   |   |
| Holguin et al. (2007)<br>Ciudad Juarez, Mexico<br>2002–2003             | N = 99, ages 6–12 yr<br>Biweekly measures for 4 mo   | Outdoor school<br>Children live 0.2–0.7 km<br>24-h avg<br>Mean: 17.5  | No quantitative results   | Correlation (r): 0.30 NO <sub>2</sub> ,<br>0.49 EC<br>Copollutant models with: NA   |
| †Carlsen et al. (2016)<br>Umea, Vasterbotten,<br>Sweden<br>Apr–Jun 2011 | N = 95, ages 11–12 yr<br>Two measures/week for 2 mo<br>973 observations  | Monitors within 1.5 km of<br>schools<br>24-h avg<br>Mean: 5.6<br>Max: 16.7  | Per 10 µg/m <sup>3</sup><br>eNO (ppb)<br>Lag 0: 1.9 (–5.8, 10)<br>Lag 0–1: 5.4 (–3.1, 13)   | Correlation (r): 0.01<br>PM <sub>10–2.5</sub> , 0.36 NO <sub>2</sub> , 0.42 O <sub>3</sub><br>Copollutant models with: NA |
| †Jacobson et al. (2012)<br>Alta Floresta, Brazil<br>Aug–Dec 2006        | N = 224, ages 8–15 yr<br>Daily measures for 4 mo   | School outdoor<br>24-h avg, 6-h avg<br>(12–6 a.m.), 12-h avg<br>(12 a.m.–noon)<br>Mean, 90th for 24-h avg<br>24.4, 44.1 | Per 10 µg/m <sup>3</sup><br>PEF (L/min)<br>24-h avg: –0.38 (–0.63, –0.13)<br>6-h avg: –0.36 (–0.66, –0.06)<br>12-h avg: –0.31 (–0.65, 0.02) | Correlation (r): NA<br>Copollutant models with: NA  |

**Table 5-12 (Continued): Epidemiologic studies of PM<sub>2.5</sub> and respiratory effects in healthy populations.**

| Study  | Study Population   | Exposure Assessment<br>Concentration in µg/m <sup>3</sup>    | Single-Pollutant Association<br>95% CI  | PM <sub>2.5</sub> Copollutant Model<br>Results and Correlations  |
|--|--|--|---|--|
| †Prieto-Parra et al.<br>(2017)<br>Santiago, Chile<br>May–Sep 2010–2011 | N = 83, ages 6–14 yr<br>Daily measures for 3 mo<br>Mean observations: 100 yr 1,<br>80 yr 2 | One monitor<br>Most children live within<br>3 km<br>Mean: 30 | OR per 10 µg/m <sup>3</sup> , lag 0–6<br>Cough: 1.22 (CI NR)<br>Three symptom index: 1.28 | Correlation ( <i>r</i> ): NA<br>Copollutant models with:<br>PM <sub>10</sub> , NO <sub>2</sub> , O <sub>3</sub> , SO <sub>2</sub> , K, Mo,<br>Pb, S, Se, and V |
| †Hong et al. (2010)<br>Seoul, South Korea<br>May–Jun 2007              | N = 92, mean (SD) age 9 (0.5) yr<br>Daily measures for 1 mo                                | Monitors in city, number NR<br>24-h avg<br>Mean: 36.2        | No quantitative results   | Correlation ( <i>r</i> ): NA<br>Copollutant models with: NA  |

Avg = average, CC16 = club cell protein, CI = confidence interval, CO = carbon monoxide, eNO = exhaled nitric oxide, FEF<sub>25–75%</sub> = forced expiratory flow between 25 and 75% of forced vital capacity, FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity, IQR = interquartile range, max = maximum, NO<sub>2</sub> = nitrogen dioxide, NO<sub>x</sub> = sum of NO<sub>2</sub> and nitric oxide, NR = not reported, O<sub>3</sub> = ozone, PEF = peak expiratory flow, PM<sub>2.5</sub> = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, *r* = correlation coefficient, SD = standard deviation, SO<sub>2</sub> = sulfur dioxide.

†Studies published since the 2009 PM ISA.

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### 5.1.7.2 Controlled Human Exposure Studies

Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided little evidence that exposure to PM<sub>2.5</sub> results in decrements in lung function in healthy populations. Although Petrovic et al. (2000) observed that a 2-hour exposure to PM<sub>2.5</sub> (92 µg/m<sup>3</sup>) resulted in decreases in thoracic gas volume, other measures of lung function (spirometry, diffusing capacity, airway resistance) were unaffected. No clear effect of short-term exposure to PM<sub>2.5</sub> on lung function was demonstrated in several studies investigating the exposure of healthy volunteers to PM<sub>2.5</sub> CAPs (Gong et al., 2003; Ghio et al., 2000; Gong et al., 2000) or urban traffic particles. In a recent study, Huang et al. (2012) exposed healthy volunteers to PM<sub>2.5</sub> CAPs collected from Chapel Hill, NC. The authors reported no changes in multiple markers of lung function (including FVC, FEV<sub>1</sub>, and FEF<sub>25-75</sub>) or in the marker for diffusion capacity DLCO at 1 and 18 hours post exposure (study details in Table 5-13).

The 2009 PM ISA (U.S. EPA, 2009) provided limited evidence that exposure to PM<sub>2.5</sub> resulted in subclinical or inflammatory effects in healthy populations. Ghio et al. (2000) reported an increase in airway and alveolar neutrophils following exposure to PM<sub>2.5</sub> CAPs. A follow-up analysis of Ghio et al. (2000) determined the increase in BALF neutrophils was associated with the Fe, SE, and SO<sub>4</sub><sup>2-</sup> content of the particulate matter (Y-CT et al., 2003). Recently, the healthy population respiratory response to PM<sub>2.5</sub> has been further examined by Behbod et al. (2013) and Huang et al. (2012). These studies involved exposure to PM<sub>2.5</sub> CAPs at either approximately 250 µg/m<sup>3</sup> (Behbod et al., 2013) or 90 µg/m<sup>3</sup> for approximately 2 hours (Huang et al., 2012) (additional study details are in Table 5-13). Multiple markers of airway inflammation were measured. Behbod et al. (2013) reported that relative to filtered air, no significant airway (sputum) responses were observed in subjects exposed to Toronto, Ontario PM<sub>2.5</sub> CAPs. Exposures to relatively lower levels of PM<sub>2.5</sub> CAPs (approximately 90 µg/m<sup>3</sup>) (Huang et al., 2012) corroborated the effects seen in the higher exposure study (Behbod et al., 2013) in that exposure to Chapel Hill NC PM<sub>2.5</sub> CAPs had no effect on IL-6, IL-8, or α1-antitrypsin in the bronchoalveolar lavage of exposed healthy subjects, although changes in blood parameters were observed (see Section 6.1.11).

**Table 5-13 Study-specific details from controlled human exposure studies of short-term PM<sub>2.5</sub> exposure and respiratory effects in healthy populations.**

| Study                                | Study Design                                     | Disease Status; n; Sex; (Age)                     | Exposure Details (Concentration; Duration; Comparison Group)  | Endpoints Measured  |
|--------------------------------------|--|---|---|---|
| <a href="#">Behbod et al. (2013)</a> | Double-blind, randomized cross-over block design | Healthy nonsmokers; n = 35; 11 M, 12 F (18–60 yr) | 234.7 µg/m <sup>3</sup> PM <sub>2.5</sub> CAPs, Toronto, ON. (IQR: 52.4 µg/m <sup>3</sup> ) for 130 min (120-min exposure + 10 min to complete tests) at rest. Comparison groups were either (1) filtered air or (2) medical air; a minimum 2-week washout period was used between exposures. | Sputum (pre- and 24-hour post-exposure): Total cell and neutrophil counts                                 |
| <a href="#">Huang et al. (2012)</a>  | Not specifically stated                          | Healthy nonsmokers; n = 23; 15 M, 8 F (20–36 yr)  | 89.5 ± 10.7 µg/m <sup>3</sup> PM <sub>2.5</sub> CAPs or 73.4 ± 9.9 µg/m <sup>3</sup> PM <sub>2.5</sub> CAPs + 0.5 ppm NO <sub>2</sub> for 2 h, Chapel Hill, NC. During exposure, subjects completed four cycles of 15 min each rest or exercise. Comparison group was clean air.              | Lung function<br>BAL (18-h post-exposure): IL-6, IL-8, α1-antitrypsin, LDH, differential leucocyte counts |

BAL = bronchoalveolar lavage; CAPs = concentrated ambient particles; IL-6 = interleukin-6; IL-8 = interleukin-8; IQR = interquartile range; LDH = lactate dehydrogenase; NO<sub>2</sub> = nitrogen dioxide.

### 5.1.7.3 Animal Toxicological Studies

#### Lung Function

1 The 2004 PM AQCD (U.S. EPA, 2004) and the 2009 PM ISA (U.S. EPA, 2009) reported several  
2 animal toxicological studies that measured pulmonary function following single or multiday exposure to  
3 PM<sub>2.5</sub> CAPs. Decreased breathing frequency (or respiratory rate) was observed in dogs exposed to PM<sub>2.5</sub>  
4 CAPs in Boston by tracheostomy exposure (Godleski et al., 2000). In addition, a strong increase in airway  
5 irritation, as indicated by decreases in end inspiratory pause and increases in end expiratory pause, pause,  
6 and enhanced pause (Penh) was observed (Nikolov et al., 2008). Increased tidal volume was found in rats  
7 exposed to PM<sub>2.5</sub> CAPs in Boston (Clarke et al., 1999) but not in New York City (Gordon et al., 2000).  
8 Increases in inspiratory and expiratory times were not seen in Wistar Kyoto rats exposed to PM<sub>2.5</sub> CAPs  
9 in Research Triangle Park, NC (Kodavanti et al., 2005). Results of these studies, showing changes in

breathing frequency and depth of breathing, indicate that short-term PM<sub>2.5</sub> exposure stimulated lung irritant responses through the activation of sensory nerves and local reflexes.

Recently, [Diaz et al. \(2013\)](#) evaluated the effects of exposure to PM<sub>2.5</sub> roadway tunnel particles on pulmonary function in Sprague Dawley rats. A 2-day exposure to tunnel particles with gases removed by a denuder resulted in increased rapid shallow breathing, as indicated by increased frequency and decreased tidal volume, minute volume, inspiratory time, and expiratory time ( $p < 0.05$ ). This breathing pattern, as well as the observed decrease in expiratory flow at 50% (EF<sub>50</sub>) ( $p = 0.01$ ), provide evidence of an irritative respiratory response. A 2-day exposure to a secondary organic aerosol formed from photochemical oxidation of primary tunnel gases (SOA) resulted in increases in pauses, including Penh ( $p \leq 0.05$ ). A 4-day exposure to SOA decreased several parameters including frequency, tidal volume, minute volume, EF<sub>50</sub>, and Vi, an indicator of respiratory drive ( $p < 0.05$ ). A 4-day exposure to photochemically aged primary particles plus SOA (P + SOA) produced the largest change in breathing parameters including decreased volumes, flow, respiratory drive, and respiratory effort ( $p < 0.05$ ). This pattern is reflective of rapid shallow breathing and suggests an irritative respiratory response with an additional effect at the thoracic level. Additional study details for this study, and other recent toxicological studies, are found in Table 5-14.

The effect of social stress on pulmonary function was examined in older Sprague Dawley rats exposed to PM<sub>2.5</sub> CAPs in Boston ([Clougherty et al., 2010](#)). In stressed animals, PM<sub>2.5</sub> CAPs exposure was associated with increased breathing frequency ( $p = 0.001$ ), lower tidal volume ( $p = 0.001$ ), lower PEF ( $p = 0.003$ ), and shorter times ( $p < 0.001$ ), suggesting rapid shallow breathing. In unstressed animals, PM<sub>2.5</sub> CAPs exposure was associated with increased PIF ( $p = 0.03$ ) and greater MV ( $p = 0.05$ ).

Effects on other pulmonary function parameters have been reported. [Amatullah et al. \(2012\)](#) found that a 4-hour exposure of BALB/c mice to PM<sub>2.5</sub> CAPs in Toronto increased quasi-static elastance of the lung ( $p < 0.05$ ). [Yoshizaki et al. \(2017\)](#) examined sex-related differences in tracheal hyperreactivity of BALB/c mice due to a multiday exposure to PM<sub>2.5</sub> CAPs in Sao Paulo, Brazil. Tracheal rings from male mice that were exposed to PM<sub>2.5</sub> CAPs were hyporesponsive to methacholine, a bronchoconstrictor, compared to tracheal rings from male mice exposed to ambient air ( $p < 0.05$ ). Tracheal rings from diestrus female mice that were exposed to PM<sub>2.5</sub> CAPs responded similarly to methacholine as tracheal rings from female mice exposed to ambient air. However, tracheal rings from estrus and proestrus female mice were hyperresponsive to methacholine compared with air controls ( $p < 0.05$ ).

**Table 5-14 Study-specific details from animal toxicologic studies of short-term PM<sub>2.5</sub> exposure and respiratory effects in healthy animals.**

| Study/Study Population   | Pollutant  | Exposure  | Endpoints   |
|--|--|---|---|
| <u>Amatullah et al. (2012)</u><br>Species: Mouse<br>Sex: Female<br>Strain: BALB/c<br>Age/weight: 6–8 weeks, 18 g                           | PM <sub>2.5</sub> CAPs<br>Toronto<br>Particle size: PM <sub>0.15–2.5</sub><br>Control: HEPA filtered air   | Route: Nose-only inhalation<br>Dose/concentration: PM <sub>0.5–2.5</sub> 254 µg/m <sup>3</sup><br>Duration: 4 h<br>Time to analysis: At end of exposure<br>Modifier: Baseline ECG   | Pulmonary function<br>BALF Cells  |
| <u>Aztatzi-Aguilar et al. (2015)</u><br>Species: Rat<br>Sex: Male<br>Strain: Sprague Dawley  | PM <sub>2.5</sub> CAPs<br>Mexico City<br>Particle size: PM <sub>2.5</sub><br>Control: Filtered air         | Route: Inhalation<br>Dose/concentration: PM <sub>2.5</sub> 178 µg/m <sup>3</sup><br>Duration: Acute 5 h/day, 3 days<br>Subchronic 5 h/day, 4 days/week, 8 weeks<br>Time to analysis: 24 h   | Gene expression and protein levels—lung tissue IL-6, components of the RAS and kallikrein-kinin endocrine system-heme oxygenase-1   |
| <u>Budinger et al. (2011)</u><br>Species: Mouse<br>Sex: Male<br>Strain: C57BL/6<br>wild type and IL-6 knockouts<br>Age/weight: 8–12 weeks  | PM <sub>2.5</sub> CAPs<br>Chicago, IL<br>Particle size: PM <sub>2.5</sub><br>Control: Filtered ambient air | Route: Whole-body inhalation<br>Dose/concentration: 88.5 ± 13.4 µg/m <sup>3</sup><br>Duration: 8 h/day for 3 days   | BALF and lung tissue-protein level and gene expression of inflammatory mediators<br>Plasma—biomarkers of coagulation  |
| <u>Chiarella et al. (2014)</u><br>Species: Mouse<br>Sex: Male<br>Strain: C57BL/6<br>wild type and Adrβ knockouts<br>Age/weight: 8–12 weeks | PM <sub>2.5</sub> CAPs<br>Chicago, IL<br>Particle size: PM <sub>2.5</sub><br>Control: Filtered ambient air | Route: Whole-body inhalation<br>Dose/concentration: 109.1 ± 6.1 µg/m <sup>3</sup><br>Duration: 8 h/day for 3 days   | BALF and lung tissue—IL-6, norepinephrine<br>Brown adipose tissue—norepinephrine  |
| <u>Clougherty et al. (2010)</u><br>Species: Rat<br>Sex: Male<br>Age/weight: 12 weeks   | PM <sub>2.5</sub> CAPs<br>Boston<br>Particle size: PM ≤ 2.5 µm<br>Control: Filtered air                    | Route: Whole-body inhalation<br>Dose/concentration: 374 µg/m <sup>3</sup><br>With large variance<br>Duration: 10 days, 5 h/day<br>Time to analysis: Respiratory data was collected during exposure at 10 min. intervals using Buxco<br>Coexposure: Stress | Pulmonary function <ul style="list-style-type: none"> <li>• Peak inspiratory flow</li> <li>• Minute volume</li> <li>• Breathing frequency</li> <li>• Inspiratory time</li> <li>• Expiratory time</li> <li>• Expiratory flows</li> <li>• Tidal volume</li> </ul> |

**Table 5-14 (Continued): Study specific details from animal toxicologic studies of short term PM<sub>2.5</sub> exposure and respiratory effects in healthy animals.**

| Study/Study Population   | Pollutant  | Exposure  | Endpoints   |
|--|--|---|---|
| <u>Diaz et al. (2013)</u><br>Species: Rat<br>Sex: Male<br>Strain: Sprague-Dawley<br>Age/weight: 250–300 g  | Roadway tunnel particles (gases removed by denuder)<br>Primary particles (P)<br>Primary particles and secondary aerosol (P-SOA)<br>Secondary organic aerosol (SOA)<br>Particle size: PM < 2.5 µm<br>Control-Filtered air (oxidizable gases, VOC and particles removed) | Route: Whole-body Inhalation<br>Dose/concentration: P-47.5 µg/m <sup>3</sup><br>P + SOA-50 µg/m <sup>3</sup><br>SOA- 48.7 µg/m <sup>3</sup><br>Duration: 2–4 days, 5 h/day<br>Time to analysis: 24 h or 48 h<br>Coexposure:<br>NO: P- 71.2 ppb<br>P + SOA- 2.1 ppb<br>SOA- 27.1 ppb<br>NOx: P- 92.6 ppb<br>P + SOA- 37.5 ppb<br>SOA- 56.9 ppb                             | BALF Cells<br>Lung function <ul style="list-style-type: none"> <li>• Tidal volume</li> <li>• Minute Volume</li> <li>• Expiratory time</li> <li>• Inspiratory time</li> <li>• Expiratory flow at 50% (flow)</li> <li>• Pause</li> <li>• Enhanced pause</li> <li>• End expiratory pause</li> <li>• End inspiratory pause</li> <li>• Peak of inspiratory flow</li> <li>• Inspiratory time</li> </ul> |
| <u>Kim et al. (2016b)</u><br>Species: Mouse<br>Strain: Balb/c<br>Sex: Male<br>Age/weight: 6–10 weeks   | DEP (NIST SRM)<br>Particle size: Not reported  | Route: Inhalation<br>Dose/concentration: 2 mg/m <sup>3</sup><br>Duration: 1 h/day for 5 days<br>Time to analysis: 9 days  | Middle ear: Gene expression microarray and pathway analysis   |
| <u>Mauderly et al. (2011)</u><br>Species: Mouse/Rat<br>Sex: Male and female<br>Strain: Mouse<br>Age/weight: C57BL/6 (10–13 weeks)<br>A/J (5–8 weeks)<br>BALB/c (3 weeks gestation, 4 weeks after birth)<br>Strain: Rat F344<br>Age/weight: (7–9 weeks) | Simulated coal emissions low, medium, high doses and high dose filtered groups<br>Particle size: Not reported in this publication. Likely PM < 2.5<br>Control: Clean air   | Route: Whole-body Inhalation<br>Dose/concentration: 1,000, 300, 100 µg/m <sup>3</sup><br>Duration: 6 mo or 1 week, 7 days/week, 6 h/day   | BALF Cells/Cytokines (F344 rats) <ul style="list-style-type: none"> <li>• MIP-2</li> <li>• Leukocytes</li> </ul>  |
| <u>Plummer et al. (2012)</u><br>Species: Mouse<br>Sex: Male<br>Strain: C57BL/6<br>Age/weight: 12–14 weeks, 25–30 g   | PM <sub>2.5</sub> CAPs from Fresno, (F, urban) or Westside (W, rural) locations in California, in two seasons (summer, winter)<br>Particle size: PM <sub>2.5</sub><br>Control: Ambient air   | Route: Whole-body inhalation<br>Dose/concentration: F/Summer 284 µg/m <sup>3</sup> , F/Winter 156 µg/m <sup>3</sup> , W/Summer 126 µg/m <sup>3</sup> , W/Winter 86 µg/m <sup>3</sup><br>Duration: 6 h/day for 10 days<br>Time to analysis: 48 hr<br>Note: Composition of PM <sub>2.5</sub> CAPs defined for organic/elemental carbon, nitrate, sulfate, ammonia, chloride | BALF cells<br>Lung tissue Cytokine/Chemokine<br>Histopathology—lung   |

**Table 5-14 (Continued): Study specific details from animal toxicologic studies of short term PM<sub>2.5</sub> exposure and respiratory effects in healthy animals.**

| Study/Study Population  | Pollutant  | Exposure   | Endpoints  |
|---|--|--|--|
| <u>Rohr et al. (2010)</u><br>Species: Rat<br>Strain: Spontaneously hypertensive (SH)<br>Wistar Kyoto (WKY)<br>Sex: Male<br>Age/weight: 11–12 weeks  | PM <sub>2.5</sub> CAPs<br>residential urban<br>Detroit, MI<br>Particle size: PM <sub>2.5</sub><br>Control: HEPA-filtered clean air | Route: Whole-body inhalation<br>Dose/concentration: 507 µg/m <sup>3</sup><br>Duration of exposure: 8 h, 13 consecutive days<br>Time to analysis: 24 h  | BALF cells<br>Lung Injury <ul style="list-style-type: none"> <li>BALF protein content</li> </ul>   |
| <u>Tyler et al. (2016)</u><br>Species: Mouse<br>Strain: C67BL/6<br>Age/weight: 6–8 weeks  | DEP, resuspended<br>Particle size: 1.5–3.0 µm ± 1.3–1.6 µm<br>Control: Filtered air  | Route: Whole-body inhalation<br>Dose/concentration: 315.3 ± 50.7 µg/m <sup>3</sup><br>Duration: 6 h  | BALF cells and cytokines<br>Particle uptake in bronchial macrophages   |
| <u>Xu et al. (2013)</u><br>Species: Mouse<br>Strain: C57BL/6<br>Sex: Male<br>Age/weight: 3 weeks  | PM <sub>2.5</sub> CAPs<br>Columbus, OH<br>Particle size: ≤PM <sub>2.5</sub><br>Control: Filtered air                               | Route: Whole-body inhalation<br>Dose/Concentration: 143.8 µg/m <sup>3</sup><br>Duration: 6 h/day, 5 days/week, 5, 14, 21 days<br>Time to analysis: Immediately post-exposure   | Immunohistochemistry—lung<br>BALF cells—flow cytometry   |
| <u>Yoshizaki et al. (2016)</u><br>Species: Mouse<br>Sex: Male and female<br>Strain: BALB/c<br>Age/Weight: 21 days                                   | PM <sub>2.5</sub> CAPs Sao Paulo, Brazil<br>Particle size: PM <sub>0.1–2.5</sub> µm<br>Control: Ambient air                        | Route: Whole-body Inhalation<br>Dose/Concentration: Cumulative dose × time<br>PM <sub>2.5</sub> : 594 ± 77 µg/m <sup>3</sup><br>Duration: Multiday<br>Coexposure: Other ambient pollutants and also PM <sub>10</sub> | Gene expression and protein levels—nasal epithelium AhR, estrogen receptor, cytochrome P450 enzymes<br>Immunohistochemistry—nasal epithelium mucus profile and mucus content |
| <u>Yoshizaki et al. (2017)</u><br>Species: Mouse<br>Sex: Male and female (diestrus, proestrus, and estrus)<br>Strain: BALB/c<br>Age/Weight: 21 days | PM <sub>2.5</sub> CAPs Sao Paulo, Brazil<br>Particle size:<br>Control: Ambient air   | Route: Whole-body Inhalation<br>Dose/Concentration: Cumulative dose × time<br>PM <sub>2.5</sub> : 600 µg/m <sup>3</sup><br>Duration: Multiday<br>Coexposure: Other ambient pollutants, PM <sub>10</sub>              | Ex vivo tracheal rings—reactivity to methacholine<br>BALF cells and cytokines<br>Lung Immunohistochemistry   |

Adrβ = beta adrenergic receptor; AhR = aryl hydrocarbon receptor; BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; DEP = diesel exhaust particles; ECG = electrocardiogram; HEPA = high-efficiency particulate absorber; IL-6 = interleukin-6; MIP-2 = macrophage inflammatory protein-2; NIST SRM = National Institute of Standards and Technology Standard Reference Material; NO = nitric oxide; NO<sub>x</sub> = oxides of nitrogen; RAS = renin-angiotensin system; VOC = volatile organic carbon.

## Pulmonary Injury

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies examined pulmonary injury and altered lung barrier/secretory function in response to single or multiday exposure to PM<sub>2.5</sub> CAPs. While increased BALF protein and lung water content were observed in rats exposed to PM<sub>2.5</sub> CAPs in Boston (Gurgueira et al., 2002; Clarke et al., 1999), injury indices were not observed in rats exposed to PM<sub>2.5</sub> CAPs in New York City and Research Triangle Park, NC (Gordon et al., 2000; Kodavanti et al., 2000). Recently, Rohr et al. (2010) exposed Wistar Kyoto rats to residential urban PM<sub>2.5</sub> CAPs in Detroit, MI for 13 days and found increased BALF protein content ( $p < 0.05$ ). Indices of injury (BALF protein and LDH activity) were not increased by any exposure to San Joaquin Valley PM<sub>2.5</sub> CAPs despite evidence of inflammation (Plummer et al., 2012). Additional study details are found in Table 5-14.

## Pulmonary Oxidative Stress

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies examined oxidative stress in response to PM<sub>2.5</sub> exposure. Increased lung chemiluminescence, activities of MnSOD and catalase, TBARS, and protein carbonyl content were reported in rats exposed to PM<sub>2.5</sub> CAPs in Boston (Rhoden et al., 2004; Gurgueira et al., 2002). Pretreatment with the thiol antioxidant N-acetylcysteine blocked PM-mediated oxidative stress in Rhoden et al. (2004). In a recent study, tissue heme oxygenase-1 activity, an index of oxidative stress, was not increased by any exposure to San Joaquin Valley PM<sub>2.5</sub> CAPs (Plummer et al., 2012) despite evidence of inflammation (Table 5-14).

## Pulmonary Inflammation

The 2004 PM AQCD (U.S. EPA, 2004) and 2009 PM ISA (U.S. EPA, 2009) reported several studies that examined the effect of single and multiday exposure to PM<sub>2.5</sub> on pulmonary inflammation. Exposure to PM<sub>2.5</sub> CAPs in Boston resulted in increased BALF neutrophils in dogs (exposed by tracheostomy) (Godleski et al., 2000) and increases in BALF neutrophils and lymphocytes in rats (Rhoden et al., 2004; Saldiva et al., 2002; Clarke et al., 1999), while BALF macrophages were decreased (Clarke et al., 1999). Godleski et al. (2002) found concentration-dependent increases in numbers of BALF neutrophils and increases in gene expression of inflammatory mediators following exposure to PM<sub>2.5</sub> CAPs in Boston. Increases in BALF total cells, neutrophils, and macrophages were also seen in rats exposed to PM<sub>2.5</sub> CAPs from Fresno, CA (Smith et al., 2003). Exposure of rats to PM<sub>2.5</sub> CAPs in New York City resulted in increased lavageable cells in one study (Zelikoff et al., 2003) and no increases in inflammatory cells in another (Gordon et al., 2000). Similarly, exposure to PM<sub>2.5</sub> CAPs in Research Triangle Park, NC had disparate effects in different studies (Kodavanti et al., 2005; Kodavanti et al., 2000). Other studies investigated the effects of exposure to traffic related air pollution, such as whole DE or GE or on-road highway aerosols, on pulmonary inflammation. However, these studies did not distinguish between effects of the gaseous or particulate parts of the mixture.

1 Similarly, recent studies are not uniform in the observation of inflammation following inhalation  
2 exposure to PM<sub>2.5</sub>. Amatullah et al. (2012) found no changes in BALF inflammatory cells immediately  
3 following a 4-hour exposure of BALB/c mice to PM<sub>2.5</sub> CAPs in Toronto (Table 5-14). No increases in  
4 BALF inflammatory cells were found in Wistar Kyoto rats exposed for 13 days to PM<sub>2.5</sub> CAPs in Detroit  
5 despite an increase in BALF protein, an index of lung injury (Rohr et al., 2010). In contrast, increases in  
6 lung tissue and BALF IL-6 were observed following multiday exposure of C57BL/6 mice to PM<sub>2.5</sub> CAPs  
7 in Chicago (Chiarella et al., 2014; Budinger et al., 2011), and Mexico City (Aztatzi-Aguilar et al., 2015).  
8 Budinger et al. (2011) also reported increases in BALF MCP-1 and TNF- $\alpha$ . In IL-6 knock-out mice,  
9 short-term PM<sub>2.5</sub> exposure failed to increase IL-6 levels, while the other two mediators were unaffected.  
10 In addition, upregulation of the IL-6 target genes surfactant protein B and tissue factor in lung tissue and  
11 thrombin-antithrombin complex in plasma was observed in wild-type, but not in IL-6 knock-out mice.  
12 These results demonstrate the involvement of lung IL-6 in mediating systemic increases in  
13 thrombin-antithrombin complex, a key mediator of thrombosis. Furthermore, increased numbers of  
14 neutrophils in the BALF were found in C57BL/6 mice exposed for 10 days to PM<sub>2.5</sub> CAPs in California  
15 ( $p < 0.05$ ) (Plummer et al., 2012). In this latter study, PM<sub>2.5</sub> CAPs were collected during two seasons  
16 (summer and winter) from an urban (Fresno) and a rural site (Westside) near Fresno. While BALF  
17 neutrophils were increased in mice exposed to Westside summer and Westside winter PM<sub>2.5</sub> CAPs  
18 ( $p < 0.05$ ), levels of KC, MCP-1 and IFN- $\gamma$  were decreased in lung tissue from mice exposed to Fresno  
19 summer PM<sub>2.5</sub> CAPs ( $p < 0.05$ ). This study demonstrates that urban and rural sites within the same  
20 airshed and season can have PM with differing ability to produce inflammation.

21 A time course study of pulmonary inflammation was conducted by Xu et al. (2013) in C57BL/6  
22 mice exposed for 5, 14, and 21 days to PM<sub>2.5</sub> CAPs in Columbus, OH. No increases in numbers of  
23 macrophages or neutrophils were found in BALF. However, immunohistochemically staining of lung  
24 tissue showed increases in macrophages (using F4/80 + as the marker) at the three time points ( $p < 0.05$ ),  
25 peaking at 5 days. No increases in neutrophils (using NIMPR14 as the marker) were seen in lung tissue.  
26 This study is unique in demonstrating early recruitment of macrophages to lung tissue in the absence of  
27 neutrophils and is indicative of innate immune system activation.

28 Other studies examined the effects of source-related PM<sub>2.5</sub> on pulmonary inflammation. Tyler et  
29 al. (2016) exposed C67BL/6 mice to resuspended DEP for 6 hours and found no increase in inflammatory  
30 cells or cytokines in the BALF and no increase in particle uptake in bronchial macrophages, despite  
31 inflammation in the hippocampus (Section 8.1.3). Diaz et al. (2013) exposed Sprague Dawley rats to three  
32 kinds of PM<sub>2.5</sub>—primary particles that were obtained directly from a tunnel with roadway gases removed  
33 by a denuder (P), secondary organic aerosol formed from photochemical oxidation of the primary tunnel  
34 gases (SOA), and photochemically aged primary particles plus SOA (P + SOA). Lymphocytes in BALF  
35 increased following 1-day exposure to P ( $p < 0.05$ ) and 2-day exposure to P + SOA ( $p < 0.07$ ), while  
36 neutrophils in BALF increased after 2-day exposure to SOA ( $p < 0.01$ ) and P + SOA ( $p < 0.05$ ). Mauderly  
37 et al. (2011) exposed mice and rats for 1 week to simulated coal emissions with and without the addition

of a particle filter. The increase in MIP-2 seen in the BALF of F344 ( $p < 0.05$ ) was prevented by filtration, indicating that the particulate part of the mixture had a role in the pro-inflammatory response.

Two of the aforementioned studies investigated the relationship between pulmonary inflammation and neurohumoral or endocrine pathways. Chiarella et al. (2014) evaluated the role of the SNS in modulating inflammation following exposure to PM<sub>2.5</sub> using knock-out mice lacking the  $\beta_2$ -adrenergic receptor specifically on macrophages. While wild type C57BL/6 mice exposed for several days to PM<sub>2.5</sub> CAPs in Chicago had increased IL-6 mRNA and protein in BALF ( $p < 0.05$ ), knock-out mice had a greatly diminished response ( $p < 0.05$ ). This finding implicates agonists of the  $\beta_2$ -adrenergic receptor, i.e., catecholamines, as partly responsible for the effects of PM<sub>2.5</sub> on IL-6 through the stimulation of  $\beta_2$ -adrenergic receptors on lung macrophages. Supporting evidence was provided by the finding that treatment with an agonist of the  $\beta_2$ -adrenergic receptor enhanced IL-6 levels in the BALF of wild type mice exposed to PM<sub>2.5</sub> ( $p < 0.05$ ). Additionally, levels of the catecholamine norepinephrine were increased in BALF and brown adipose tissue following PM<sub>2.5</sub> exposure ( $p < 0.05$ ), indicative of increased sympathetic tone. Taken together, results of this study provide evidence that exposure to PM<sub>2.5</sub> activated the sympathetic nervous system, which enhanced the release of IL-6 from lung macrophages. Downstream effects of macrophage-derived IL-6 on thrombosis were also examined (see Section 6.1.12).

Aztatzi-Aguilar et al. (2015) evaluated the RAS and kallikrein-kinin endocrine system in the lung in Sprague Dawley rats exposed for several days to PM<sub>2.5</sub> CAPs in Mexico City. Increased protein expression of IL-6 in lung tissue ( $p < 0.05$ ) was accompanied by increased expression of the angiotensin I receptor gene, reduced angiotensin I receptor protein levels, and increased angiotensin converting enzyme mRNA levels ( $p < 0.05$ ). Protein levels of angiotensin converting enzyme and mRNA levels of angiotensin II receptor mRNA were not impacted. In addition, PM<sub>2.5</sub> CAPs exposure resulted in increased mRNA levels for kallikrein-1 enzyme ( $p < 0.05$ ). Kallikrein-1 is a serine protease enzyme required to produce kinin peptides, which are necessary to activate bradykinin receptors. The RAS mediates vasoconstriction and vascular oxidative stress and inflammation and is counterbalanced by the kallikrein-kinin endocrine system via bradykinin-mediated production of nitric oxide, an important vasodilator. The SNS is known to regulate the endocrine systems. Although not specifically examined in this study, PM<sub>2.5</sub> exposure-mediated activation of the SNS activation may link PM<sub>2.5</sub> exposure and the RAS.

## Morphology

As described in the 2009 PM ISA (U.S. EPA, 2009), several studies found that exposure to PM<sub>2.5</sub> CAPs in Boston, MA resulted in mild morphological changes in the lung including hyperplasia of the terminal bronchiolar and alveolar ductal epithelium and pulmonary arteriolar edema (Rhoden et al., 2004; Batalha et al., 2002; Saldiva et al., 2002). Recently, Yoshizaki et al. (2016) evaluated the effects of multiday exposure to Sao Paulo, Brazil PM<sub>2.5</sub> CAPs on nasal epithelium in male and female BALB/c mice. The influence of estrus cycle in female was also determined. PM<sub>2.5</sub> CAPs exposure resulted in an

1 increase in acidic mucus content in males and a decrease in acidic mucus content in females ( $p < 0.05$ )  
2 (Table 5-14). PM<sub>2.5</sub> CAPs exposure had no effect on neutral mucus content in either male or female mice.  
3 In addition, estrus cycle had no effect on mucus content or response to PM<sub>2.5</sub> CAPs exposure.  
4 Upregulation of message and protein levels of estrogen, aryl hydrocarbon receptors, and cytochrome  
5 P450 proteins was examined in nasal epithelium. PM<sub>2.5</sub> CAPs exposure resulted in decreased mRNA  
6 levels of estrogen receptor  $\beta 2$  and cytochrome 1b1 in female mice ( $p < 0.01$ ). Female rats in diestrus, but  
7 not estrus or proestrus, exhibited decreased mRNA levels of estrogen receptor  $\beta 2$ , cytochrome 1b1, and  
8 cytochrome 1a2 ( $p < 0.05$ ). Estrogen receptor protein levels were decreased in nasal epithelium and aryl  
9 hydrocarbon receptor protein levels were increased in submucosal gland by PM<sub>2.5</sub> CAPs exposure in  
10 female mice ( $p < 0.05$ ). Only female rats in estrus not diestrus or proestrus) exhibited these changes  
11 ( $p < 0.05$ ).

### Allergic Sensitization

12 The 2009 PM ISA (U.S. EPA, 2009) described numerous studies demonstrating the adjuvant  
13 potential of PM. While most of these studies involved intra-nasal or other noninhalation routes of  
14 exposure, one inhalation study demonstrated a strong adjuvant effect of PM (Whitekus et al., 2002). In  
15 this study, mice were exposed to resuspended DEP and subsequently challenged with OVA.  
16 OVA-specific IgG1 and IgE were enhanced by DEP exposure in the absence of general markers of  
17 inflammation. This effect, as well as DEP-mediated lipid peroxidation and protein oxidation, was blocked  
18 by pretreatment with the thiol antioxidants N-acetylcysteine and bucillamine. These results indicate that  
19 oxidative stress played a role in DEP-mediated allergic sensitization. Recent studies that have become  
20 available since the last review, while supportive of the adjuvant potential of PM<sub>2.5</sub>, involve noninhalation  
21 routes of exposure (i.e., subcutaneous, intra-peritoneal and oropharyngeal aspiration).

### Pathways Related to Otitis Media

22 Kim et al. (2016b) conducted a transcriptomic analysis in the middle ear following exposure to  
23 DEP (Table 5-14). BALB/c mice were exposed to resuspended DEP for several days and gene expression  
24 microarray and pathway analysis were performed on tissue collected 9 days later. In the middle ear,  
25 numerous genes were upregulated or downregulated because of DEP exposure. Pathway analysis  
26 identified several of these genes as potential biomarkers for DEP-related otitis media including  
27 cholinergic receptor muscarinic 1, erythropoietin, son of sevenless homolog 1, estrogen receptor 1, cluster  
28 of differentiation 4, and interferon  $\alpha$  1.

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#### 5.1.7.4 Summary of Respiratory Effects in Healthy Populations

Similar to results described in the 2009 PM ISA (U.S. EPA, 2009), evaluation of the current epidemiologic evidence indicates that short-term PM<sub>2.5</sub> exposures are inconsistently related to respiratory effects in healthy adults. Where there is supporting evidence, changes tend to be transient and confounding by copollutants is inadequately examined. For general community daily average exposures, there is some consistent epidemiologic evidence for PM<sub>2.5</sub>-related respiratory effects in healthy children, but the evidence is limited in number for any one particular endpoint. In addition to the limited supporting evidence, uncertainties remain as to whether short-term PM<sub>2.5</sub> exposure leads to overt and persistent respiratory effects in healthy populations or is related to such effects across a wide range of PM<sub>2.5</sub> concentrations.

Controlled human exposure and animal toxicological studies also examined pulmonary function and inflammation responses to short-term exposure to PM<sub>2.5</sub> CAPs. While evidence from controlled human exposure studies was inconsistent, animal toxicological studies clearly demonstrated changes in pulmonary function and inflammation. Recent evidence supports the previously observed involvement of lung irritant responses in mediating the changes in respiratory function, such as rapid shallow breathing, seen following exposure to PM<sub>2.5</sub>. BALF cellular infiltrates are commonly found following exposure to PM<sub>2.5</sub> and appear to primarily involve recruitment of macrophages and neutrophils into the airways. In addition, several studies implicate changes in various cytokines in BALF and lung tissue. Increases in numbers of specific macrophages in lung tissue provides evidence for the activation of innate immunity over several days to several weeks. Pulmonary injury and oxidative stress responses were inconsistent. However, a study evaluated in the 2009 PM ISA demonstrated oxidative stress-mediated allergic sensitization due to inhalation of PM<sub>2.5</sub>. Different regions of the respiratory tract are impacted by short-term PM<sub>2.5</sub> exposure with morphologic changes observed in the terminal bronchiolar and alveolar regions and changes in mucus profile found in nasal epithelium. A mechanistic study shows involvement of the SNS in augmenting macrophage-mediated inflammatory effects following exposure to PM<sub>2.5</sub>. In addition, the RAS and kallikrein-kinin endocrine system in the lung were impacted by short-term exposure to PM<sub>2.5</sub>.

Variability in results observed in controlled human exposure and animal toxicological studies could be due to the time points assessed (too long after exposure), the nature of the exposures (dose, particle composition), the sensitivity of the model (species, strain, age, predisposing factors) and the sensitivity of the measurements used. When PM<sub>2.5</sub> CAPs are used, the composition of the PM, which is related to source and season, could add to this variability. Finally, whether the exposure was a single time or repeated could have a large effect. Repeated exposures, even those less than 30 days, may trigger adaptive physiologic and cellular responses that are not present for very short term single exposure studies, such as single acute exposures.

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## 5.1.8 Respiratory Effects in Populations with Cardiovascular Disease

Given the prevalence of cardiovascular disease in the general population and the inter-relationships between the cardiovascular and respiratory systems, numerous animal toxicological studies have been conducted in animal models of cardiovascular disease. Many of these studies were evaluated in the 2004 PM AQCD and the 2009 PM ISA (U.S. EPA, 2009). Pulmonary function responses were examined following single and multiday exposure of hypertensive rats to PM<sub>2.5</sub> CAPs from New York, Research Triangle Park, NC, Taiwan, and Boston, MA (Kodavanti et al., 2005; Lei et al., 2004; Nadziejko et al., 2002; Godleski et al., 2000). Alterations in tidal volume and breathing frequency were found, indicating the involvement of lung irritant receptors and the triggering of local reflexes in the response to short-term PM<sub>2.5</sub> exposure. Multiday exposure of SH rats to PM<sub>2.5</sub> CAPs in the Netherlands altered levels of BALF CC16 in a concentration-dependent manner (Kooter et al., 2006). CC16 is a secretory product of nonciliated bronchiolar Club cells and is a marker of injury and thought to contribute to the control of inflammation. However, there was no evidence of pulmonary injury (as assessed by BALF LDH levels) in this study or another study involving PM<sub>2.5</sub> CAPs in Research Triangle Park, NC (Kodavanti et al., 2005). Kooter et al. (2006) also found that a multiday exposure of SH rats to PM<sub>2.5</sub> CAPs in the Netherlands increased levels of heme oxygenase-1, an indicator of oxidative stress. Several studies in hypertensive rats evaluated pulmonary inflammation following exposure to PM<sub>2.5</sub> CAPs. While some studies found increased numbers of inflammatory cells in BALF (and even a correlation between PM<sub>2.5</sub> CAPs concentrations and numbers of neutrophils) (Cassee et al., 2005; Lei et al., 2004), others did not (Kooter et al., 2006; Kodavanti et al., 2005). Campen et al. (2006) found a concentration-dependent effect on inflammation in PM<sub>2.5</sub> exposed-ApoE knockout mice, a model of atherosclerosis.

A few recent studies add to this evidence base (Table 5-15). Rohr et al. (2010) exposed SH rats to PM<sub>2.5</sub> CAPs in Detroit and found no evidence of lung injury as assessed by BALF protein levels. Farraj et al. (2015) studied the effect of a 4-hour exposure of SH rats to PM<sub>2.5</sub> CAPs in two seasons, summer and winter, in Research Triangle Park, NC. Activities of LDH, glutathione S transferase, and CuZn SOD, indicators of injury and oxidative stress, were decreased by exposure to summer PM<sub>2.5</sub> CAPs but not winter PM<sub>2.5</sub> CAPs ( $p \leq 0.05$ ). PM<sub>2.5</sub> CAPs concentration was higher in summer than in winter, but metal exposure concentrations were roughly equivalent. Concomitant exposure to 200 ppb O<sub>3</sub> appeared to have little additional effect on these parameters. No effects on inflammation were found by Rohr et al. (2010) or Farraj et al. (2015). Furthermore, Tyler et al. (2016) conducted an inhalation exposure of ApoE knockout mice to resuspended DEP and found no increase in inflammatory cells or cytokines in the BALF and no increase in particle uptake in bronchial macrophages, despite inflammatory effects in the hippocampus (Section 8.1.3). Overall, short-term PM<sub>2.5</sub> exposure results in pulmonary effects in some studies but not others. The most consistent evidence is for changes in pulmonary function.

**Table 5-15 Study-specific details from animal toxicological studies of short-term PM<sub>2.5</sub> exposure and respiratory effects in models of cardiovascular disease.**

| Study/Study Population   | Pollutant  | Exposure   | Endpoints   |
|--|--|--|---|
| <u>Farraj et al. (2015)</u><br>Species: Rat<br>Sex: Male<br>Strain: SH<br>Age/Weight: 12 weeks   | PM <sub>2.5</sub> CAPs<br>Research Triangle Park, NC<br>Particle size: 324 nm summer, 125 nm winter<br>Control: Filtered air | Route: Whole-body inhalation<br>Dose/Concentration: 85-170 µg/m <sup>3</sup><br>Duration: 4 h<br>Time to analysis: 24 hr<br>Modifier: Telemeter implanted, summer and winter | Lung Injury—BALF LDH activity<br>Inflammation—BALF cells<br>BALF antioxidant enzymes—GST and CuZn SOD |
| <u>Rohr et al. (2010)</u><br>Species: Rat<br>Strain: Spontaneously hypertensive (SH)<br>Wistar Kyoto (WKY)<br>Sex: Male<br>Age/Weight: 11–12 weeks | PM <sub>2.5</sub> CAPs<br>residential urban<br>Detroit, MI<br>Particle sizes: PM <sub>2.5</sub>                              | Route: Whole-body inhalation<br>Dose/Concentration: 507 µg/m <sup>3</sup><br>Duration of exposure: 8 h, 13 consecutive days<br>Time to analysis: 24 h                        | BALF cells<br>Lung Injury <ul style="list-style-type: none"> <li>BALF protein content</li> </ul>      |
| <u>Tyler et al. (2016)</u><br>Species: Mouse<br>Strain: ApoE knockout<br>Age/Weight: 6–8 weeks   | DEP, resuspended<br>Particle size: 1.5–3.0 µm ± 1.3–1.6 µm<br>Control: Filtered air  | Route: Whole-body inhalation<br>Dose/Concentration: 300 µg/m <sup>3</sup><br>Duration: 6 h   | BALF cells and cytokines<br>Particle uptake in bronchial macrophages                                  |

ApoE = Apolipoprotein E; BALF = bronchoalveolar lavage fluid; CAPs = concentrated ambient particles; CuZn SOD = copper, zinc superoxide dismutase; GST = glutathione S transferase; LDH = lactate dehydrogenase; SH = spontaneously hypertensive.

### 5.1.9 Respiratory Mortality

Studies that examine the association between short-term PM<sub>2.5</sub> exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for PM<sub>2.5</sub>-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. The multicity epidemiologic studies evaluated in the 2009 PM ISA provided evidence of consistent positive associations, ranging from 1.0–2.2% for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations, between short-term PM<sub>2.5</sub> exposure and respiratory mortality (U.S. EPA, 2009). However, compared to associations between short-term PM<sub>2.5</sub> exposure and cardiovascular and total (nonaccidental) mortality, confidence intervals were larger due to respiratory mortality comprising a smaller percentage of all mortalities. Across studies, the PM<sub>2.5</sub> effect on respiratory mortality was observed to be immediate with associations occurring in the range of lag 0 to 2 day(s). A limitation within the evidence was that multicity studies did not extensively examine potential copollutant confounding, but evidence from

single-city studies suggested that the PM<sub>2.5</sub>-respiratory mortality relationship was not confounded by gaseous copollutants. Additionally, there was limited coherence across epidemiologic and controlled human exposure studies, which complicated the interpretation of the associations observed for short-term PM<sub>2.5</sub> exposure and respiratory mortality.

Recent multicity epidemiologic studies along with meta-analyses provide additional evidence of generally consistent positive associations between short-term PM<sub>2.5</sub> exposure and respiratory mortality (Figure 11-2). In addition to providing evidence that supports the rather immediate timing of respiratory mortality effects (i.e., lag 0 to 1 days), some recent studies also provide initial evidence that respiratory mortality effects due to short-term PM<sub>2.5</sub> exposure may be more prolonged (i.e., lags >2 days). Unlike the studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), some recent studies have also further evaluated the PM<sub>2.5</sub>-respiratory mortality relationship by examining cause-specific respiratory mortality outcomes (i.e., COPD, pneumonia, and LRTI) (Samoli et al., 2014; Janssen et al., 2013). Overall, the results reported in the studies that examine cause-specific respiratory mortality outcomes are generally consistent with the results for all respiratory mortality, but the smaller number of mortality events observed results in unstable estimates with larger uncertainty.

Evidence to further characterize the PM<sub>2.5</sub>-respiratory mortality relationship is also provided by recent epidemiologic studies. Overall, these studies continue to support a relationship between PM<sub>2.5</sub> and respiratory mortality and provide additional evidence that: gaseous pollutants do not confound the PM<sub>2.5</sub>-respiratory mortality relationship; PM<sub>2.5</sub> effects on respiratory mortality may not be limited to the first few days after exposure; the magnitude of the association tends to be largest during warmer months; and there is inconsistent evidence that temperature extremes modify associations between short-term PM<sub>2.5</sub> exposure and respiratory mortality (see Section 5.1.10).

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### 5.1.10 Policy-Relevant Considerations

Epidemiologic studies that examined short-term PM<sub>2.5</sub> exposure and respiratory-related effects often conduct additional analyses to assess whether the associations observed are due to chance, confounding, or other biases. Within this section, evidence is evaluated across epidemiologic studies to further assess the association between short-term PM<sub>2.5</sub> exposure and respiratory-related effects, focusing specifically on those analyses that address policy-relevant issues: copollutant confounding (Section 5.1.10.1), model specification (Section 0), lag structure (Section 5.1.10.3), the role of season and temperature on PM<sub>2.5</sub> associations (Section 5.1.10.4), averaging time of PM<sub>2.5</sub> concentrations (Section 5.1.10.5), and concentration-response (C-R) and threshold analyses (Section 5.1.10.6). The studies that inform these issues are primarily epidemiologic studies that conducted time-series or case-crossover analyses focusing on respiratory-related ED visits and hospital admissions and respiratory mortality. Studies examining additional endpoints, such as subclinical markers of a PM-related respiratory

effect (e.g., lung function, inflammation, etc.), may also examine some of these issues, but are not the focus of this evaluation.

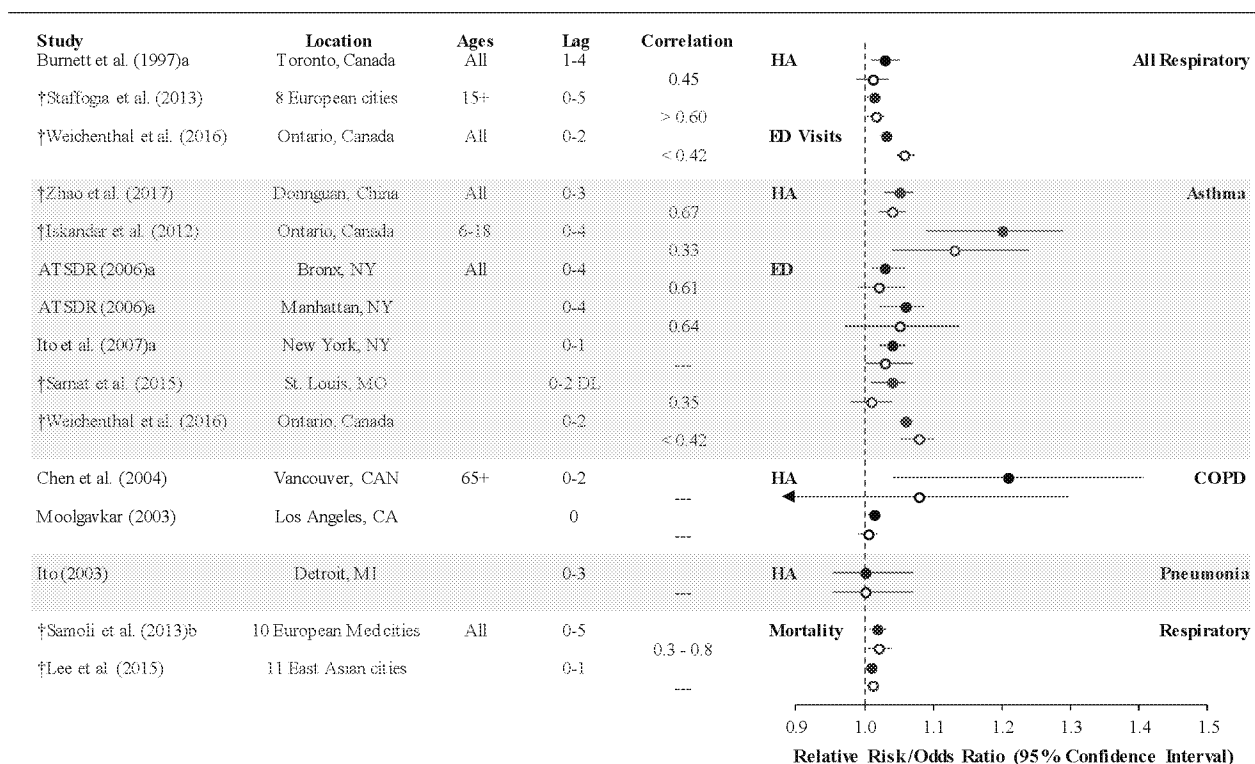
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#### 5.1.10.1 Examination of Potential Copollutant Confounding

The potential confounding effect of copollutants is a previously identified source of uncertainty in the examination of the relationship between short-term PM<sub>2.5</sub> exposure and respiratory effects, and thus requires careful consideration particularly with respect to whether the magnitude and direction of PM<sub>2.5</sub> risk estimates change in copollutant models. Compared to the evidence available at the completion of the 2009 PM ISA, many recent studies conducted analyses that inform whether the relationship between short-term PM<sub>2.5</sub> exposures and respiratory-related effects, specifically hospital admissions, ED visits, and respiratory mortality, may be confounded by copollutants. Recent studies have examined the potential for copollutant confounding by evaluating copollutant models that include O<sub>3</sub> (Figure 5-9), NO<sub>2</sub> (Figure 5-10), SO<sub>2</sub> (Figure 5-11), CO (Figure 5-12) and PM<sub>10-2.5</sub> (Figure 5-13). These recent studies address a previously identified data gap by informing the extent to which effects associated with exposure to PM<sub>2.5</sub> are independent of coexposures to correlated copollutants. Generally, these studies provide evidence that the association between short-term PM<sub>2.5</sub> exposures and respiratory health outcomes is robust to the inclusion of copollutants in a statistical model. This evidence provides support for an independent association between PM<sub>2.5</sub> concentrations and respiratory-related effects.

Building off studies evaluated in the 2009 PM ISA, recent studies that examined the potential confounding effects of O<sub>3</sub> on associations between short-term PM<sub>2.5</sub> exposure and respiratory-related outcomes continue to report correlations between O<sub>3</sub> and PM<sub>2.5</sub> ranging from low (<0.4) to high (>0.7). Across the respiratory-related outcomes examined, where positive associations with PM<sub>2.5</sub> were reported in single-pollutant models, associations were often attenuated in copollutant models, but remained positive. The most extensive evaluation of potential copollutant confounding was for studies focusing on asthma hospital admissions and ED visits, where recent studies report results that are consistent with those observed in studies evaluated in the 2009 PM ISA (Figure 5-9). Additionally, recent evidence provides additional support for positive PM<sub>2.5</sub> associations with hospital admissions and ED visits for all respiratory diseases as well as initial evidence indicating that PM<sub>2.5</sub> associations with respiratory mortality are relatively unchanged in copollutant models with O<sub>3</sub>. While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were generally persistent, although in some cases attenuated, in copollutant models with O<sub>3</sub>. Individual panel study results from copollutant models with O<sub>3</sub> are discussed within the relevant endpoint sections (Section 5.1.2.2, Section 0, and Section 5.1.7.1).

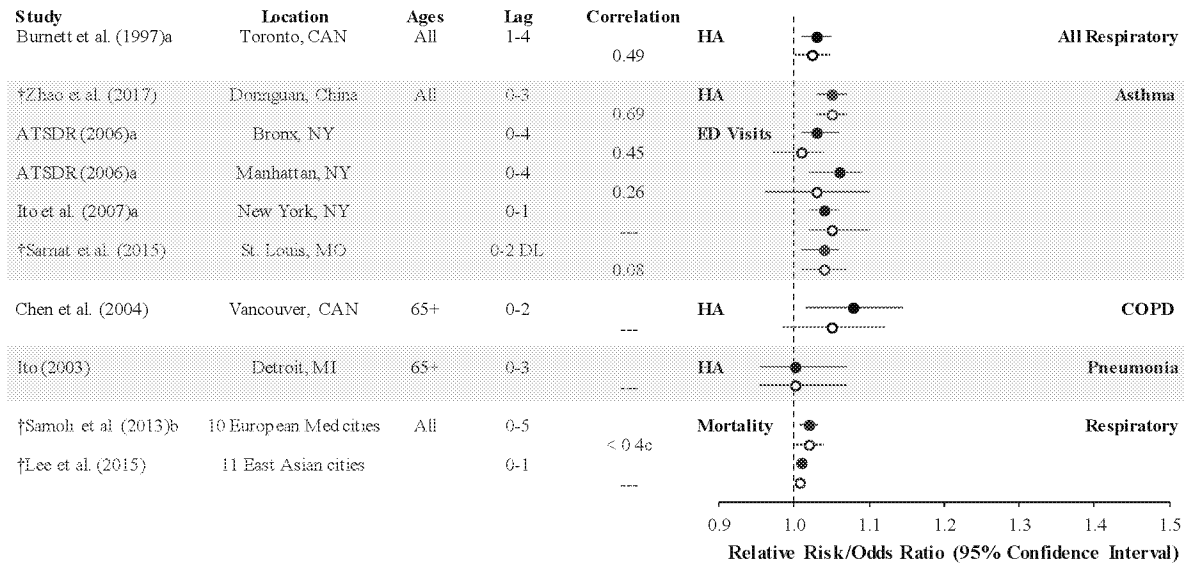




Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0–5 days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-10 Summary of associations for short-term PM<sub>2.5</sub> exposure and respiratory-related outcomes from copollutant models with NO<sub>2</sub> for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

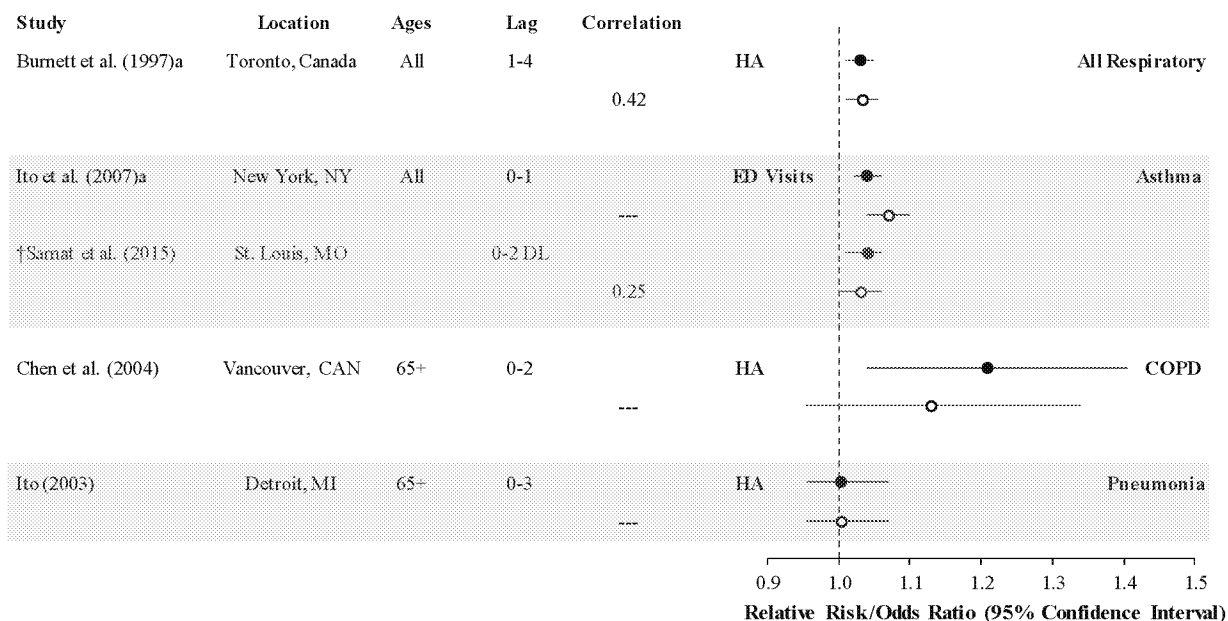
The examination of potential copollutant confounding by SO<sub>2</sub> on the relationship between short-term PM<sub>2.5</sub> exposure and respiratory-related outcomes is similar to that observed for O<sub>3</sub> and NO<sub>2</sub>, with most of the evidence from studies examining asthma hospital admissions and ED visits (Figure 5-11). Across studies, correlations between PM<sub>2.5</sub> and SO<sub>2</sub> were primarily <0.5. Most of the studies that examined copollutant models with SO<sub>2</sub> were evaluated in the 2009 PM ISA, but recent studies add to the evidence base for asthma hospital admissions and ED visits further demonstrating that associations are relatively unchanged in copollutant models with SO<sub>2</sub>, while also providing new evidence for respiratory mortality. While panel studies infrequently reported results from copollutant models, adverse associations reported across several endpoints were generally persistent, although in some cases attenuated, in copollutant models with SO<sub>2</sub>. Individual panel study results from copollutant models with SO<sub>2</sub> are discussed within the relevant endpoint sections (Section 0, Section 5.1.2.4, Section 5.1.4.2, Section 5.1.4.4, and Section 5.1.7.1).



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. a = copollutant analyses for warm season only; b = copollutant analysis only conducted for lag 0–5 days; c = correlations were <0.4 in all cities except Milan and Turin where it was ~0.6. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-11 Summary of associations for short-term PM<sub>2.5</sub> exposure and respiratory-related outcomes from copollutant models with sulfur dioxide (SO<sub>2</sub>) for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

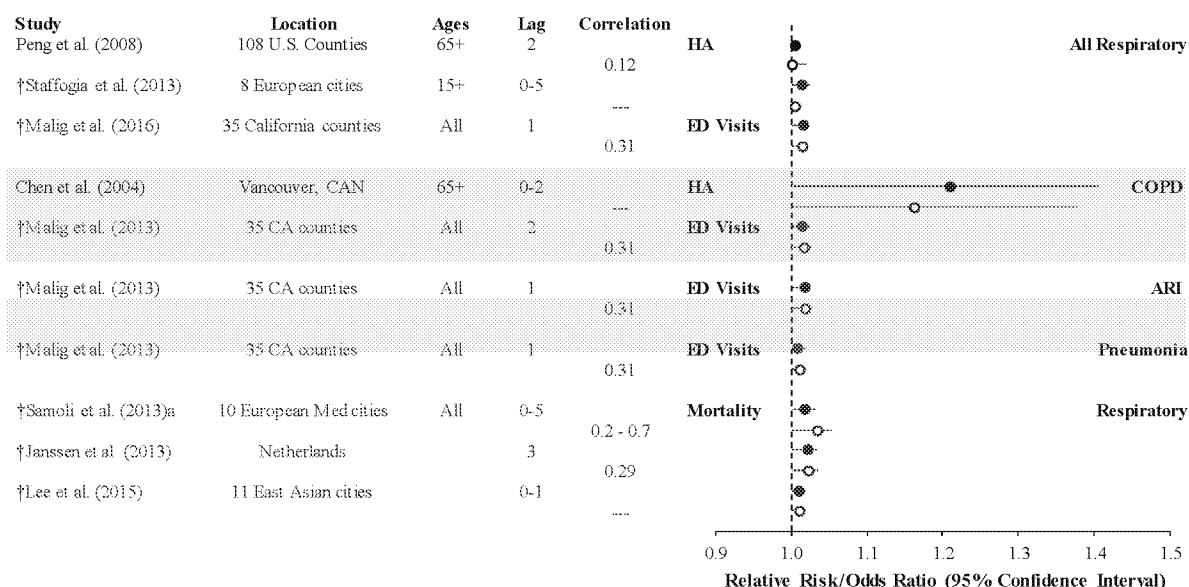
Compared to O<sub>3</sub>, NO<sub>2</sub>, and SO<sub>2</sub> the assessment of potential copollutant confounding by CO has not been extensively examined in recent studies (Figure 5-12). However, across the studies evaluated in the 2009 PM ISA, along with the recent study conducted by Sarnat et al. (2015) examining asthma ED visits, evidence indicates that in studies that observed positive associations with PM<sub>2.5</sub>, the association was relatively unchanged in copollutant models with CO.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.  
a = copollutant analyses for warm season only. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-12 Summary of associations for short-term PM<sub>2.5</sub> exposure and respiratory-related outcomes from copollutant models with carbon monoxide (CO) for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

Recent studies also greatly expand upon the examination of potential copollutant confounding by PM<sub>10-2.5</sub> (Figure 5-13). Across the studies evaluated, correlations between PM<sub>2.5</sub> and PM<sub>10-2.5</sub> were primarily low ( $r < 0.4$ ). PM<sub>2.5</sub> associations for all respiratory-related outcomes are generally unchanged in models that adjust for PM<sub>10-2.5</sub>. However, an uncertainty across studies that examined either single- or copollutant models that include PM<sub>10-2.5</sub> is the variety of methods employed to estimate PM<sub>10-2.5</sub> concentrations and the potential measurement error associated with each method (Section 2.5.1.2.3 and Section 3.3.1.1).



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA.  
a = copollutant analysis only conducted for lag 0-5. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

**Figure 5-13 Summary of associations for short-term PM<sub>2.5</sub> exposure and respiratory-related outcomes from copollutant models with PM<sub>10-2.5</sub> for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations.**

In conclusion, since the 2009 PM ISA, there has been growth in the number of studies that examined potential confounding of the relationship between short-term PM<sub>2.5</sub> exposure and respiratory-related outcomes by copollutants. These recent studies provide additional evidence supporting that PM<sub>2.5</sub> associations are relatively unchanged, although in some instances attenuated as well as increased, in copollutant models with gaseous and particle pollutants.

#### 5.1.10.1.1 PM<sub>2.5</sub> within the Multipollutant Mixture

Although copollutant models are important in assessing potential copollutant confounding, it is well known that collinearity between pollutants can result in unstable estimates and that air masses are not limited to just two pollutants (Dominici et al., 2010). Therefore, in addition to copollutant models, studies that examine multipollutant exposures can provide additional information on the role of PM<sub>2.5</sub> within the complex air pollution mixture.

Analyses of pollutant mixtures, which use an array of statistical methods and pollutant combinations, for respiratory-related effects have focused on asthma ED visits. These studies indicate

1 increases in asthma ED visits when ambient concentrations of PM<sub>2.5</sub> and a copollutant(s) are  
2 simultaneously high, but do not clearly show a larger increase than with PM<sub>2.5</sub> alone. In analyses  
3 conducted in Atlanta (Winquist et al., 2014a) and then subsequently for the entire state of Georgia (Xiao  
4 et al., 2016), PM<sub>2.5</sub> was a priori grouped with the other criteria pollutants (i.e., O<sub>3</sub>, CO, NO<sub>2</sub>, and SO<sub>2</sub>) to  
5 examine their joint effect on pediatric asthma ED visits. In both studies, PM<sub>2.5</sub> was associated with  
6 pediatric asthma ED visits in single-pollutant models. However, in Xiao et al. (2016) joint effect models  
7 were relatively similar to the single-pollutant model, but in Winquist et al. (2014a) the joint effect model  
8 results were much larger (quantitative results only presented for warm season, no interaction model)  
9 (Table 5-16). Instead of defining air pollution mixtures a priori, other analyses examined whether there  
10 were groups of days with similar pollution profiles, specifically days representative of high and low air  
11 pollution exposures based on quartiles of PM<sub>2.5</sub>, NO<sub>2</sub>, CO, and O<sub>3</sub> concentrations using a classification  
12 and regression tree (C&RT) approach. This approach was used to examine associations between high and  
13 low air pollution days and asthma in Atlanta, GA; St. Louis, MO; and Dallas, TX. In Atlanta, GA, Gass et  
14 al. (2014) reported that RRs with PM<sub>2.5</sub> were largest in magnitude for days when PM<sub>2.5</sub> concentrations  
15 were in the highest quartile, while NO<sub>2</sub> was in the lowest two quartiles, as well as days when both NO<sub>2</sub>  
16 and PM<sub>2.5</sub> were in higher quartiles. Gass et al. (2015) expanded the analysis of Gass et al. (2014) to  
17 include Atlanta, GA; St. Louis, MO; and Dallas, TX. The authors observed that pollution profiles varied  
18 across cities resulting in the overall quartiles of pollutant concentrations for a particular mixture  
19 sometimes differing from the distribution of concentrations within an individual city. For example, PM<sub>2.5</sub>  
20 concentrations were in the 4th quartile for one city, but the overall mixture across cities showed that PM<sub>2.5</sub>  
21 concentrations were in the 1st quartile. Gass et al. (2015) reported evidence of mixtures with high PM<sub>2.5</sub>  
22 concentrations having the association largest in magnitude, but associations were similar in magnitude in  
23 instances when PM<sub>2.5</sub> concentrations were in the lowest quartile. While the other multipollutant studies  
24 focused on examining combinations of pollutants at different parts of the individual pollutant  
25 concentration distribution, Toti et al. (2016) in Houston, TX focused on pollutant concentrations on same  
26 and successive days that are in the 4th quartile of each pollutant concentration distribution. Across the  
27 different combinations, as well as those that included PM<sub>2.5</sub>, the authors reported ORs that were relatively  
28 similar in magnitude. In contrast with U.S. cities, the association between asthma ED visits and an air  
29 quality health index (AQHI), which combines PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub> based on mortality risk, in Windsor,  
30 ON, appears to be influenced by either PM<sub>2.5</sub> or O<sub>3</sub>, depending on the lag (Szyszkowicz and Kousha,  
31 2014). The OR for the AQHI was similar to that of O<sub>3</sub> at lag 0 and that of PM<sub>2.5</sub> at lags 4 and 5 (Table 5-  
32 16). Whereas the previous studies evaluated focused on multipollutant mixtures, Weichenthal et al. (2016)  
33 examined whether there was evidence of effect modification of the PM<sub>2.5</sub>-asthma ED visit association in  
34 15 Ontario cities. The authors observed that the PM<sub>2.5</sub> association increased with increasing city-level  
35 oxidative potential of PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub> combined (Weichenthal et al., 2016).

36 In summary, the studies that examined multipollutant mixtures that include PM<sub>2.5</sub> indicate that  
37 mixtures encompassing days with high PM<sub>2.5</sub> concentrations are often those mixtures with the highest risk  
38 estimates. Additionally, when comparing single-pollutant PM<sub>2.5</sub> results with those based on mixtures, the

- 1 risk estimate associated with the mixture is relatively similar and, in some cases, larger than that observed
- 2 for PM<sub>2.5</sub>.

**Table 5-16 Combined influence of PM<sub>2.5</sub> and copollutants on emergency department (ED) visits for asthma.**

| Study  | PM <sub>2.5</sub> Single-Pollutant OR RR<br>95% CI  | Combined OR or RR (95% CI)   |
|--|---|--|
| †Xiao et al. (2016)<br>Georgia, 2002–2008  | Per 6.9 µg/m <sup>3</sup><br>1.03 (1.02, 1.04); lag 0–2   | Joint Effect Model, Criteria Pollutants Combination (O <sub>3</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , and PM <sub>2.5</sub> ); lag 0–2 per IQR increase in each pollutant<br>No interactions: 1.03 (1.01, 1.05)<br>Interactions: 1.06 (1.02, 1.09)   |
| †Winquist et al. (2014a)<br>Atlanta, GA, 1998–2004   | Per 9.2 µg/m <sup>3</sup> , warm season<br>1.04 (1.02, 1.07)  | Joint Effect Model, Criteria Pollutant Combination (O <sub>3</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , and PM <sub>2.5</sub> )<br>Warm season, no interactions: 1.13 (1.06, 1.21)  |
| †Gass et al. (2014)<br>Atlanta, GA, 1999–2009  | NR  | C&RT to group days by PM <sub>2.5</sub> , NO <sub>2</sub> , O <sub>3</sub> and CO quartiles<br>Q1 PM <sub>2.5</sub> , NO <sub>2</sub> , CO, and O <sub>3</sub> : 1.0 (reference)<br>Q4 PM <sub>2.5</sub> , Q1–4 O <sub>3</sub> , Q1 or 2 NO <sub>2</sub> , Q1–4 CO: 1.10 (1.05, 1.16)<br>Q4 PM <sub>2.5</sub> , Q1–3 O <sub>3</sub> , Q3 NO <sub>2</sub> , Q1–4 CO: 1.08 (1.01, 1.15)<br>Q1 PM <sub>2.5</sub> , Q1–4 O <sub>3</sub> , Q3 or 4 NO <sub>2</sub> , Q1–4 CO: 1.08 (1.03, 1.14) |
| †Gass et al. (2015)<br>Atlanta, GA, 1999–2009<br>St. Louis, MO, 2001–2007<br>Dallas, TX, 2006–2008 | NR  | C&RT to group days by PM <sub>2.5</sub> , NO <sub>2</sub> and O <sub>3</sub> quartiles<br>Q1 PM <sub>2.5</sub> , NO <sub>2</sub> , and O <sub>3</sub> : 1.0 (reference)<br>Q4 PM <sub>2.5</sub> , Q3 O <sub>3</sub> , Q1 or 2 NO <sub>2</sub> : 1.07 (1.03, 1.12)<br>Q1 PM <sub>2.5</sub> , Q3 O <sub>3</sub> , Q3 or 4 NO <sub>2</sub> : 1.04 (0.99, 1.08)<br>Q1–4 PM <sub>2.5</sub> , Q4 O <sub>3</sub> , Q3 NO <sub>2</sub> : 1.05 (1.01, 1.09)   |
| †Toti et al. (2016)<br>Houston, TX, 2006–2012  | NR  | Association rule mining to estimate ORs for all PM <sub>2.5</sub> , O <sub>3</sub> , NO <sub>2</sub> , SO <sub>2</sub> , CO and lag 0 to 4-day combinations and identify unique, statistically significant ORs.<br>Q1–3 of each pollutant in combination: 1.0 (reference)<br>Q4 PM <sub>2.5</sub> lag 0 and Q4 O <sub>3</sub> lag 0: 1.20 (1.02, 1.41)<br>Q4 PM <sub>2.5</sub> lag 0, Q4 NO <sub>2</sub> lag 0 and Q4 O <sub>3</sub> lag 2: 1.33 (1.00, 1.65)                              |
| †Szyszkowicz and Kousha (2014)<br>Windsor, ON, Canada 2004–2010                                    | Per IQR (not reported) increase<br>Lag 0: 1.02 (0.97, 1.06)<br>Lag 3: 1.03 (0.99, 1.08)<br>Lag 4: 1.05 (1.01, 1.09) | AQHI combining PM <sub>2.5</sub> , O <sub>3</sub> and NO <sub>2</sub> (per 1 unit)<br>Lag 0: 1.03 (0.99, 1.07)<br>Lag 3: 1.02 (0.98, 1.06)<br>Lag 4: 1.04 (1.01, 1.08)   |

**Table 5-16 (Continued): Combined influence of PM<sub>2.5</sub> and copollutants on emergency department (ED) visits for asthma.**

| Study  | PM <sub>2.5</sub> Single-Pollutant OR RR<br>95% CI         | Combined OR or RR (95% CI)  |
|--|--|---|
| †Weichenthal et al.<br>(2016)<br>15 cities Ontario,<br>Canada<br>2004–2011 | Lag 0–2 avg, per 10 µg/m <sup>3</sup><br>1.06 (1.05, 1.07) | Effect modification by oxidative potential of PM <sub>2.5</sub> , NO <sub>2</sub><br>and O <sub>3</sub><br>Q1: 1.02 (0.99, 1.04)<br>Q2: 1.06 (1.00, 1.13)<br>Q3: 1.08 (0.97, 1.19)<br>Q4: 1.10 (1.05, 1.15) |

AQHI = air quality health index, C&RT = classification and regression tree, CO = carbon monoxide, NO<sub>2</sub> = nitrogen dioxide, O<sub>3</sub> = ozone, OR = odds ratio, RR = relative risk, SO<sub>2</sub> = sulfur dioxide.

†Studies published since the 2009 PM ISA.

1

### 5.1.10.2 Model Specification

2 An underlying uncertainty in the interpretation of epidemiologic study results is the difference in  
3 the magnitude and precision, and sometimes direction, of risk estimates across studies. It has remained  
4 difficult to elucidate why there are differences in risk estimates, but it is often thought to reflect the  
5 different statistical models used in each study. However, it has also been hypothesized that other factors  
6 may also be contributing to these observed differences such as differences in PM<sub>2.5</sub> composition or  
7 demographics between study locations (e.g., Section 11.6.3).

8 Recent epidemiologic studies have conducted sensitivity analyses to assess whether PM<sub>2.5</sub>  
9 associations with respiratory-related outcomes are dependent on the statistical model employed, in an  
10 attempt to reduce potential biases in observed associations. Such sensitivity analyses assess the influence  
11 of alternative model specifications, such as increasing degrees of freedom (df) to account for temporal  
12 trends, or the inclusion of alternative weather covariates. Collectively, recent studies that examined model  
13 specification provide evidence that PM<sub>2.5</sub> associations are generally robust to increasing the df per year to  
14 account for temporal trends, but in some cases attenuation of the association was observed when these  
15 additional df were included. Additionally, studies reported that PM<sub>2.5</sub> associations are relatively  
16 unchanged regardless of the weather covariates included in statistical models (i.e., different weather  
17 variables or lag days and df specified for the weather variables). Collectively, these studies reduce the  
18 uncertainty associated with the differences in the magnitude and direction of risk estimates in  
19 epidemiologic studies potentially resulting from the different statistical models employed across studies.

20 Several studies examined different approaches to control for seasonality or temporal trends by  
21 either increasing or decreasing the df/year used in studies of short-term PM<sub>2.5</sub> exposure and  
22 respiratory-related effects. PM<sub>2.5</sub>-associated increases in asthma hospital admissions and ED visits were  
23 consistently observed when different df/year were used to account for temporal trends. For example,  
24 studies conducted in several U.S. cities reported that PM<sub>2.5</sub> associations remained robust to alternative

degrees of freedom (2–28 df/year) for temporal trends ([Alhanti et al., 2016](#); [Sarnat et al., 2015](#); [Kim et al., 2012](#); [Silverman and Ito, 2010](#)). When examining all respiratory-related hospital admissions and ED visits, an examination of the control for temporal trends was limited to a few studies, all of which were conducted in Europe, ([Stafoggia et al., 2013](#)), in eight European cities, and ([Lanzinger et al., 2016b](#)), in the UFireg project. [Stafoggia et al. \(2013\)](#) provided evidence that uniformly applying the same df/year across all cities could underestimate the PM<sub>2.5</sub> association. This was reflected by comparing results for models where 8 df/year was applied to each city or the df/year applied to each city was selected by minimizing the absolute value of the sum of the partial autocorrelation functions (PACF) to the base model, which employed a three-way interaction between year, month, and day of week to account for temporal trends. The authors reported that using 8 df/year attenuated the association while the PACF approach, which resulted in df/year ranging from 3–9 for each city, resulted in relatively unchanged PM<sub>2.5</sub> risk estimates. However, [Lanzinger et al. \(2016b\)](#) reported that PM<sub>2.5</sub> associations were relatively unchanged in models employing 3, 4, or 6 df/year to account for temporal trends.

In addition to conducting sensitivity analyses that examine control for temporal trends, some studies also assessed whether associations between short-term PM<sub>2.5</sub> exposure and respiratory-related hospital admissions and ED visits were sensitive to alternative weather covariates. Altering the lags (e.g., 0, 2-day average) for temperature and humidity in New Jersey ([Gleason et al., 2014](#)), or adjusting for maximum temperature in Atlanta, GA and St. Louis, MO ([Alhanti et al., 2016](#)) resulted in PM<sub>2.5</sub> associations that were relatively unchanged. [Stafoggia et al. \(2013\)](#) also examined the influence of including a longer temperature lag (i.e., 0–6 days) in the model to account for the potential prolonged effects of temperature on respiratory diseases. Replacing the 0–1-day lag temperature covariate with a 0–6-day lag term resulted in a relatively similar effect (lag 0–1: 1.36% [95% CI: 0.23, 2.49]; lag 0–6: 1.48% [95% CI: 0.29, 2.69]).

While most studies examined the influence of model specification on PM<sub>2.5</sub> associations with respiratory-related effects by focusing specifically on the inclusion of alternative weather covariates in statistical models, a few studies conducted analyses to examine whether there was evidence of model misspecification and potential residual confounding. In studies conducted in Atlanta, GA ([Strickland et al., 2010](#)) and St. Louis, MO ([Sarnat et al., 2015](#)), model misspecification was evaluated by examining associations with PM<sub>2.5</sub> concentrations on the day after an asthma ED visit (lag –1 day). In both studies the results of the base model are relatively similar to those reported for lag –1 day (i.e., ([Strickland et al., 2010](#)), warm season: RR = 1.05 [95% CI: 1.02, 1.08], lag 0–2, RR = 1.03 [95% CI: 1.00, 1.05], lag –1; ([Sarnat et al., 2015](#)), all-year: RR = 1.04 [95% CI: 1.01, 1.06], lag 0–2, RR = 1.02 [95% CI: 0.99, 1.04], lag –1). The smaller association, closer to the null in both studies, indicates that potential confounders of the relationship between short-term PM<sub>2.5</sub> exposure and asthma ED visits were adequately accounted for in the statistical model.

Across studies that examined alternative model specifications, replacing covariates used in the base model to account for the confounding effects of weather did not result in measurable changes in

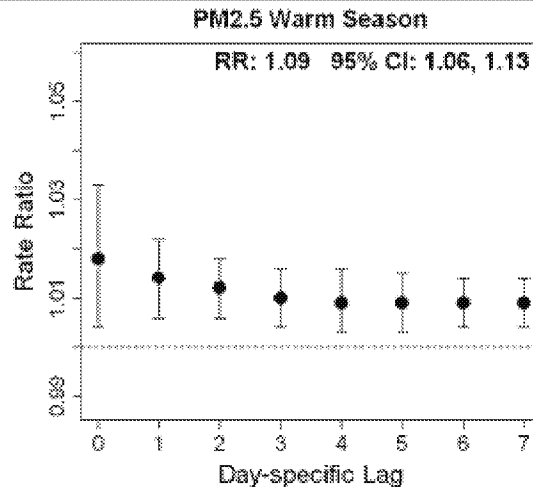
PM<sub>2.5</sub> associations for respiratory-related effects. Additionally, there was little evidence that increasing the df/year to account for temporal trends influenced PM<sub>2.5</sub> associations; however, initial evidence indicates that applying the same df/year across individual cities in a multicity study may contribute to underestimating PM<sub>2.5</sub> risk estimates.

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### 5.1.10.3 Lag Structure

An examination of associations between short-term PM<sub>2.5</sub> exposure and respiratory-related effects across different lag days can inform whether PM<sub>2.5</sub> elicits an immediate, delayed, or prolonged effect on health. As detailed throughout this chapter, evidence from studies that examine respiratory-related hospital admissions and ED visits indicates positive associations across single-day as well as multiday lags ranging from 0 to 4 days. However, to date many studies have not systematically evaluated different lags to examine the timing of effects, specifically whether there is evidence of an immediate (lag 0–1), delayed (lag 2–5), or prolonged (lag 0–5) PM<sub>2.5</sub> effect. An examination of lag structure in recent studies focusing on asthma, COPD, respiratory infections, and all respiratory-related hospital admissions and ED visits indicates that the strongest association in terms of magnitude and precision is generally within a few days after exposure for each of these outcomes, but there is some evidence demonstrating the potential for a prolonged PM<sub>2.5</sub> effect.

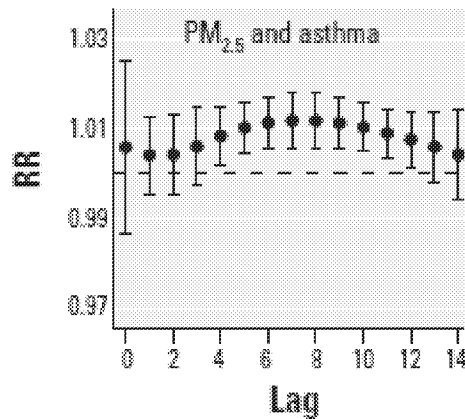
Among children in Atlanta, GA (Strickland et al., 2010) and individuals of all ages in Denver, CO (Kim et al., 2012), the pattern of associations for PM<sub>2.5</sub>-asthma ED visits varied. In Strickland et al. (2010), lag 0 was reported to have the association largest in magnitude, but positive associations persisted across single-day lags of 1 to 7 days (Figure 5-14).



Source: Permission pending, [Strickland et al. \(2010\)](#).

**Figure 5-14** Rate ratio and 95% confidence intervals for individual lag days from a constrained cubic polynomial distributed lag model examining associations between short-term PM<sub>2.5</sub> exposure and pediatric asthma emergency department (ED) visits in Atlanta, GA.

In contrast to the relatively immediate effect observed in [Strickland et al. \(2010\)](#), [Kim et al. \(2012\)](#) reported positive associations across the full range of lags examined (0–14), with the strongest associations, in terms of magnitude and precision, observed at lags 4 to 12 days, indicating a potential delayed response to short-term PM<sub>2.5</sub> exposure ([Figure 5-15](#)). When examining a distributed lag model of 0 to 7 days in Adelaide, Australia, [Chen et al. \(2016\)](#) observed an inconsistent pattern of associations with the strongest associations for asthma hospital admissions occurring at lags 2 and 4 days. When comparing results from multiday averages and distributed lag models, risk estimates were found to be larger in magnitude for the distributed lag model in Atlanta, GA ([Strickland et al., 2010](#)) (lag 0–2: RR = 1.05 [95% CI: 1.02, 1.08]; lag 0–7 DL: RR = 1.10 [95% CI: 1.07, 1.14]), but a similar magnitude of an association was observed at shorter and longer distributed lag models in St. Louis, MO ([Sarnat et al., 2015](#)) (lag 0–2: 1.04 [95% CI: 1.01, 1.06]; lag 0–4 DL: RR = 1.04 [95% CI: 1.01, 1.08]).



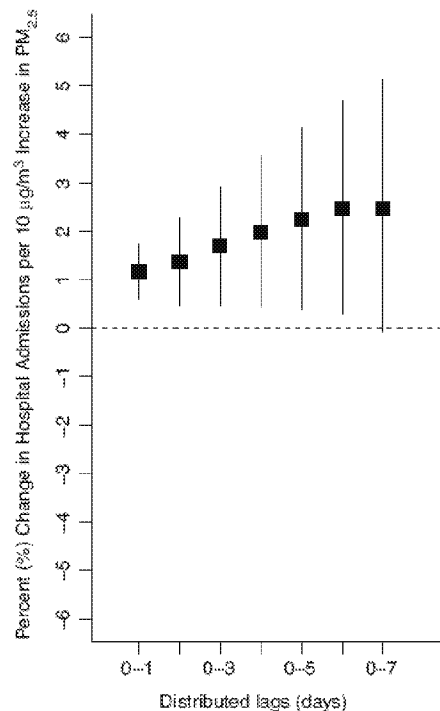
Source: Permission pending, Kim et al. (2012).

**Figure 5-15** Relative risk and 95% confidence intervals for individual lag days from a constrained distributed lag model examining associations between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions in Denver, CO.

Compared to asthma, the assessment of associations across different lags was limited for COPD and respiratory infection. Belleudi et al. (2010) examined both single-day and multiday lags (0 to 6 days, 0–1, 0–2, 0–5, and 0–6) for both COPD and lower respiratory tract infections. For COPD, the authors reported positive associations across a few single-day lags with the strongest association in terms of magnitude and precision observed at lag 0 (1.88% [95% CI: –0.27, 4.09]) and 2 (1.76 [95% CI: –0.18, 3.73]), with no evidence of an association for any of the multiday lags examined. However, for lower respiratory tract infections, positive associations were observed across single-day lags ranging from 1 to 5 days, but the magnitude of the association varied with the largest magnitude at lags 2 (2.82%) and 3 (3.04%). The multiple single-day lags reporting positive associations was further reflected when examining multiday averages, which provide evidence of a prolonged effect of short-term PM<sub>2.5</sub> exposure on lower respiratory tract infection (lag 0–5: (3.71 [95% CI: –0.57, 8.17]); lag 0–6: (3.62 [95% CI: –0.96, 8.42])).

Associations across different lags were further evaluated in recent studies focusing on all respiratory-related hospital admissions and ED visits. Overall, consistent, positive associations are reported across a range of single-day lags in multiple multicity studies (Bravo et al., 2017; Lanzinger et al., 2016b; Samoli et al., 2016a; Jones et al., 2015; Stafoggia et al., 2013). Some recent studies examined associations over a range of single-day lags through either a traditional single-day lag model or a distributed lag model. For example, Samoli et al. (2016a) and Jones et al. (2015) examined a series of single-day lags and reported positive association that were similar in magnitude across each individual lag, but confidence intervals were wide. In contrast to Samoli et al. (2016a) and Jones et al. (2015), Kim et al. (2012) did not report evidence of an association between short-term PM<sub>2.5</sub> exposure and

respiratory-related hospital admissions when examining the individual lag days of a 0 to 14 day constrained distributed lag model. However, the results for combinations of respiratory-related diseases differ from those observed for asthma hospital admissions in [Kim et al. \(2012\)](#) where, as previously mentioned, positive associations were observed at lags 4 to 12 days. In single-day lags of 0 to 2 days [Bravo et al. \(2017\)](#) reported a 0.79% increase (95% CI: 0.62, 0.97) at lag 0 in hospital admissions, but no evidence of an association at lags 1 or 2. However, when examining a distributed lag model of 0–7 days, the magnitude of the association increased as lag days increased, but confidence intervals did as well, providing some evidence of a potential prolonged PM<sub>2.5</sub> effect ([Figure 5-16](#)).



Source: Permission pending, [Bravo et al. \(2017\)](#).

**Figure 5-16** Percent increase in respiratory-related hospital admissions for a distributed lag model up to 0–7 days for a 10 µg/m<sup>3</sup> increase in 24-hour average PM<sub>2.5</sub> concentrations across 708 U.S. counties.

The results of [Bravo et al. \(2017\)](#) are consistent with both [Lanzinger et al. \(2016b\)](#) and [Stafoggia et al. \(2013\)](#) where positive associations were observed across each of the lags examined with the association with the largest magnitude observed for lag 0–5 in both studies. [([Lanzinger et al., 2016b](#)): 2.8%, lag 0–1; 5.1%, lag 2–5; and 6.0%, lag 0–5; ([Stafoggia et al., 2013](#)): 0.49, lag 0–1; 1.1%, lag 2–5; and 1.4%, lag 0–5].

1 The assessment of associations across different lag structures for short-term PM<sub>2.5</sub> exposure and  
2 respiratory morbidity is further informed by analyses focusing on respiratory mortality. Multicity  
3 epidemiologic studies that examined cause-specific mortality in the 2009 PM ISA observed immediate  
4 effects with consistent positive associations for respiratory mortality at lags ranging from 0 to 2 days;  
5 however, these lags were selected a priori. [Lippmann et al. \(2013b\)](#), within the NPACT study, and  
6 [Janssen et al. \(2013\)](#), in a study conducted in the Netherlands, examined PM<sub>2.5</sub>-respiratory mortality  
7 associations at single-day lags ranging from 0 to 3 days. While [Lippmann et al. \(2013b\)](#) reported the  
8 strongest association at lag 1, [Janssen et al. \(2013\)](#) reported evidence of associations larger in magnitude  
9 and with greater precision up to 3 days. [Stafoggia et al. \(2017\)](#), examining single-day lags ranging from 0  
10 to 10 days, provide evidence that potentially supports the pattern of associations observed in both  
11 [Lippmann et al. \(2013b\)](#) and [Janssen et al. \(2013\)](#). The authors reported evidence of an immediate effect  
12 at lag 1, but also evidence of positive associations similar in magnitude at lags 3, 6, and 7 (quantitative  
13 results not presented). However, confidence intervals were wide, complicating the comparison of results  
14 across studies.

15 An examination of multiday lags by [Lee et al. \(2015\)](#) found a similar magnitude of an association  
16 across lags ranging from 0–1 to 0–4 days, which is consistent with the results of the studies examining  
17 single-day lags. However, [Samoli et al. \(2013\)](#), when examining lags indicative of immediate, delayed,  
18 and prolonged effects, reported evidence of an immediate PM<sub>2.5</sub> effect on respiratory mortality (0.72%  
19 [95% CI: –0.11, 1.6]; lag 0–1) that was larger in magnitude at longer lags (lag 2–5: 1.6% [95% CI: 0.62,  
20 2.7]; lag 0–5: 1.9% [95% CI: 0.7, 3.1]). These results were further confirmed when examining single-day  
21 lags in a polynomial distributed lag model of 0–7 days, where associations were relatively consistent in  
22 magnitude from 0 to 2 days and then steadily increased out to 7 days.

23 Across the respiratory-related hospital admission and ED visit and mortality studies evaluated  
24 that conducted systematic evaluations of PM<sub>2.5</sub> associations across a range of lags, recent studies further  
25 support studies evaluated in the 2009 PM ISA that provided evidence of associations at lags ranging from  
26 0–5 days. Studies of respiratory morbidity, specifically asthma and all respiratory-related hospital  
27 admissions and ED visits, along with more limited evidence from studies of COPD and respiratory  
28 infection, support that longer PM<sub>2.5</sub> exposures (i.e., 0–5-day lags) are associated with respiratory-related  
29 effects. Studies of respiratory mortality tended to support more immediate PM<sub>2.5</sub> effects (i.e., lags of 0 to  
30 2 days), but initial evidence of stronger associations, in terms of magnitude and precision, at lags of  
31 0–5 days is consistent with the pattern of associations observed in the hospital admission and ED visit  
32 studies.

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#### 5.1.10.4 The Role of Season and Temperature on PM<sub>2.5</sub> Associations

33 The examination of seasonal differences in PM<sub>2.5</sub> associations within studies that focus on  
34 respiratory-related hospital admissions and ED visits, as well as respiratory mortality, can provide

information that could be used to assess whether specific sources that vary by season are contributing to the PM<sub>2.5</sub> associations observed in all-year analyses. Additional studies that examine potential modification of PM<sub>2.5</sub> associations by temperature can further elucidate the impact of season on observed associations. Studies evaluated in the 2009 PM ISA, demonstrated seasonal variability in PM<sub>2.5</sub> associations with respiratory-related effects with some studies reporting associations in warmer months while others in colder months, which is further supported by recent studies. Fewer recent studies have examined potential modification of PM<sub>2.5</sub> associations by temperature.

#### 5.1.10.4.1 Season

Recent studies have further examined the role of season on the relationship between short-term PM<sub>2.5</sub> exposure and respiratory-related effects, with the most extensive analyses focusing on asthma and all respiratory-related hospital admissions and ED visits. In studies of respiratory-related hospital admissions and ED visits, most often the warm season was defined as April–September, particularly for most northern U.S. cities, but in some cases the warm months encompassed May–October, such as for Atlanta, GA. PM<sub>2.5</sub>-associated increases in asthma ED visits were observed in New Jersey in studies restricted to the warm season (Gleason and Fagliano, 2015; Gleason et al., 2014). Seasonal differences in associations are also supported by Malig et al. (2013) in a study of 35 California counties and asthma ED visits, which reported associations larger in magnitude in the warm compared to the cold season, as well as Stafoggia et al. (2013), in a study of eight European cities, which examined whether associations between short-term PM<sub>2.5</sub> exposure and all respiratory-related hospital admissions in the warm season were larger in magnitude than those observed in the all-year analysis. When restricting the analysis to the warm season (April–September), Stafoggia et al. (2013) reported a larger percent increase in respiratory-related hospital admissions (4.49% [95% CI: 1.72, 7.35]; lag 0–5) compared to the all-year analysis (1.36% [95% CI: 0.23, 2.49]; lag 0–5).

An examination of associations between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions and ED visits in the cold season in U.S. locations were null except in New York, NY (Silverman and Ito, 2010; Ito et al., 2007). Additionally, (Rodopoulou et al., 2014) in a study examining all respiratory disease and acute respiratory infection ED visits in New Mexico, (Belleudi et al., 2010) in a study conducted in Rome, Italy focusing on respiratory infection ED visits, and (Lanzinger et al., 2016b) in a study of four European cities focusing on all respiratory-related hospital admissions reported evidence of associations larger in magnitude in the cold versus the warm season. The pattern of seasonal associations was also found to differ between two Australian cities, with an association larger in magnitude in the warm season in Sydney (Jalaludin et al., 2008) and in the cold season in Adelaide (Chen et al., 2016).

Additional studies conducted more refined analyses, focusing on all four seasons, to examine potential seasonal differences in PM<sub>2.5</sub> associations with respiratory-related hospital admissions and ED visits. For studies of asthma hospital admission and ED visit, an examination of PM<sub>2.5</sub> associations by the

four seasons is limited to Detroit, MI and Seoul, South Korea, but are consistent with each other in showing associations only in the spring (i.e., March–May) (Li et al., 2011; Kim, 2015, 3012210). However, studies focusing on all respiratory-related hospital admissions and ED visits reported a slightly different pattern of associations. Zanobetti et al. (2009), in a study of 26 U.S. counties reported the largest association in the spring (4.34% [95% CI: 2.19, 6.54]; lag 0–1) with the percent increase in respiratory-related hospital admissions ranging from 1.26–1.79% in the other seasons. Jones et al. (2015), in a study of New York state observed a slightly different pattern of associations across the seasons than Zanobetti et al. (2009). Focusing on lag 1, the authors reported associations largest in magnitude in the summer and fall with little evidence of an association in the winter and spring. Bell et al. (2015), in a study of 213 U.S. counties observed stronger associations with respiratory tract infection hospital admissions in spring (0.80% [95% CI: 0.02, 1.58]) and winter (0.40% [95% CI: –0.29, 1.10]), compared to the fall and spring where no evidence of an association was reported. The results from studies examining all four seasons support the results from studies that reported stronger associations during the warm season, but also provide some evidence that the greatest risk of PM<sub>2.5</sub>-related respiratory effects may span into months traditionally defined as representing the cold season.

While studies in the 2009 PM ISA focusing on respiratory morbidity conducted seasonal analyses, studies focusing on mortality were limited to total (nonaccidental) mortality. These studies generally reported larger associations in warmer months (see Section 11.1.6.1) but resulted in uncertainty as to whether the same pattern of associations exists for cause-specific mortality, including respiratory mortality.

Recent multicity studies conducted in the U.S. (Dai et al., 2014; Lippmann et al., 2013a), Europe (Pascal et al., 2014; Samoli et al., 2013), and Asia (Lee et al., 2015) examined whether there was evidence of seasonal differences in the PM<sub>2.5</sub>-respiratory mortality relationship. Within the NPACT study (Lippmann et al., 2013a), the examination of seasonal PM<sub>2.5</sub> associations resulted in a pattern of associations consistent with what was observed for total mortality (i.e., associations larger in magnitude during the warm season). However, compared to the all-year analysis, there was evidence of positive associations in the warm season across all lags examined with associations similar in magnitude (~0.5% increase) at lags 0, 1, and 3 days. There was also evidence of a positive association with respiratory mortality during the cold season, but only at lag 1 (0.40% [95% CI: –0.34, 1.1]). Dai et al. (2014), in a study of 75 U.S. cities reported results that were generally consistent with Lippmann et al. (2013a), but examined associations across all four seasons. Across seasons, the PM<sub>2.5</sub>-respiratory mortality association was largest in magnitude during the spring (4.0% [95% CI: 2.9, 5.2]; lag 0–1), with positive, but smaller associations across the other seasons ranging from 0.58–1.1%.

Additional studies conducted in Europe report results consistent with those studies conducted in the U.S. In the MED-PARTICLES project, Samoli et al. (2013) examined short-term PM<sub>2.5</sub> exposure and respiratory mortality at lag 0–5 days and reported associations larger in magnitude in the warm season (6.5% [95% CI: 2.6, 10.5]) compared to the cold (1.7% [95% CI: 0.27, 3.2]). In France, Pascal et al.

(2014) reported similar results, but in an analysis of all four seasons. Associations between short-term PM<sub>2.5</sub> exposure and respiratory mortality were only positive during the spring and summer seasons, but confidence intervals were wide (quantitative results not presented).

Although the studies that examined U.S. and European cities provide consistent evidence of PM<sub>2.5</sub>-respiratory mortality associations being larger in magnitude during warmer months (i.e., spring and summer), a study conducted in 11 east Asian cities observed a different pattern of associations. Lee et al. (2015) reported that PM<sub>2.5</sub> associations with respiratory mortality were larger in the cold season (1.3% [95% CI: 0.38, 2.2]) compared to the warm (0.63% [95% CI: -0.21, 1.5]). It is unclear why these results differ from the other studies, but mean PM<sub>2.5</sub> concentrations and mean temperature tended to be higher across the cities in Lee et al. (2015) compared to the cities in the other studies evaluated in this section.

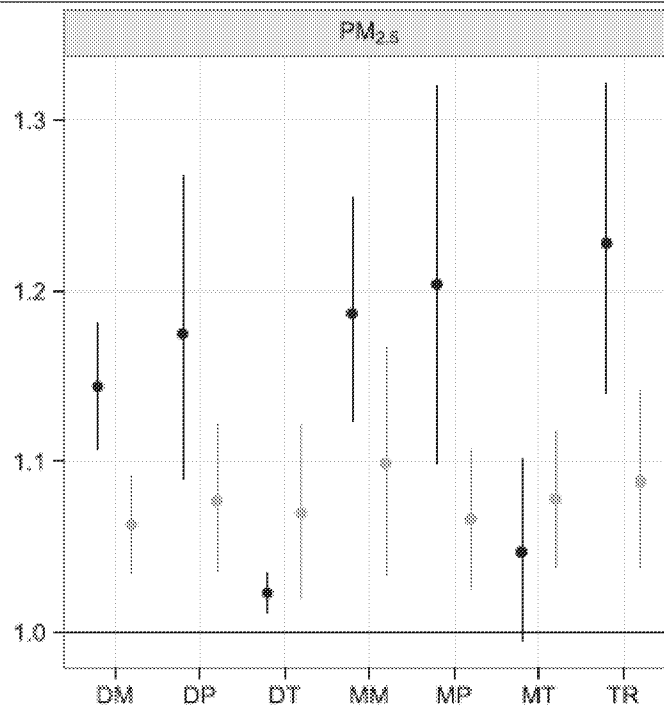
Across the multicity studies that examined seasonal associations, compared to studies of respiratory morbidity, results indicate that associations between short-term PM<sub>2.5</sub> exposure and respiratory mortality tend to be larger in magnitude during warmer parts of the year (i.e., spring and summer), specifically in locations where mean PM<sub>2.5</sub> concentrations and temperature are more like those observed in the U.S. These results are supported by studies that conducted more refined examinations of seasonal associations by each of the four seasons and observed associations larger in magnitude in the spring and summer.

In addition to traditional analyses that examine whether PM<sub>2.5</sub>-respiratory-related hospital admission and ED visit associations vary by season; other studies have examined whether specific weather patterns influence associations. Hebbern and Cakmak (2015), in a study conducted in 10 Canadian cities, examined the association between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions and whether the association was modified by specific synoptic weather patterns. Individual days were grouped into synoptic weather types based on temperature, humidity, and other factors. PM<sub>2.5</sub> associations with asthma hospital admissions were reported to be largest in magnitude for days classified as moist polar and transitional types and lowest in magnitude for dry tropical and moist tropical days, but interestingly these latter categories had higher PM<sub>2.5</sub> concentrations. However, when adjusting for aeroallergens, Hebbern and Cakmak (2015) observed that the difference in associations between weather types were absent.

## Aeroallergens

While seasonal analyses can inform whether PM<sub>2.5</sub>-asthma hospital admission and ED visit associations are influenced by weather, another factor tangentially related that has a strong seasonal component is aeroallergens. As detailed above, Hebbern and Cakmak (2015) reported that PM<sub>2.5</sub>-asthma hospital admissions varied by synoptic weather pattern, but not when controlling for aeroallergens. However, in the models that controlled for aeroallergens, the RRs across all weather types, although attenuated, remained positive and were relatively similar, ranging from approximately 1.05–1.1 (Figure

5-17). Instead of controlling for the potential confounding effects of aeroallergens, [Gleason et al. \(2014\)](#), in a study conducted in New Jersey, examined whether the PM<sub>2.5</sub>-asthma ED visit association varied across PM<sub>2.5</sub> quintiles depending on high and low levels of tree, grass, weed, and ragweed pollen. The authors observed no evidence of effect modification across the quintiles for high and low tree and grass pollen levels, and across all quintiles and levels of ragweed except for the combination of high ragweed and the highest quintile of PM<sub>2.5</sub> concentrations. However, when examining high ragweed pollen levels, as PM<sub>2.5</sub> concentrations increased there was evidence of effect modification ([Table 5-17](#)).



Note: Black circles represent before and grey circles represent after adjustment for aeroallergens.  
 DM = dry moderate; DP = dry polar; DT = dry tropical; MM = moist moderate; MP = moist polar; MT = moist tropical;  
 TR = transitional weather types.  
 Source: Permission pending, [Hebborn and Cakmak \(2015\)](#).

**Figure 5-17 Pooled relative risks across 10 Canadian cities by synoptic weather category.**

**Table 5-17 Odds ratios for quintile analyses in Gleason et al. (2014) from single-pollutant PM<sub>2.5</sub> analyses and analyses examining effect modification by high weed pollen days.**

| Study  | PM <sub>2.5</sub> Analysis OR (95% CI)   | Effect Modification Analysis OR (95% CI)  |
|--|--|---|
| † <u>Gleason et al. (2014)</u><br>New Jersey, whole state<br>2004–2007 | Lag 0:<br>0.53–6.1 µg/m <sup>3</sup> : 1.0 (reference)<br>6.1–8.5 µg/m <sup>3</sup> : 1.0 (0.95, 1.06)<br>8.5–11.4 µg/m <sup>3</sup> : 0.99 (0.94, 1.04)<br>11.4–16.8 µg/m <sup>3</sup> : 1.01 (0.96, 1.06)<br>>16.9 µg/m <sup>3</sup> : 1.05 (0.99, 1.11) | Effect modification of PM <sub>2.5</sub> associations by high weed pollen levels (lag 0–2) by PM <sub>2.5</sub> quintiles (lag 0):<br>0.53–6.1 µg/m <sup>3</sup> : 1.0 (reference)<br>6.1–8.5 µg/m <sup>3</sup> : 1.57 (1.14, 2.17)<br>8.5–11.4 µg/m <sup>3</sup> : 1.53 (1.11, 2.12)<br>11.4–16.8 µg/m <sup>3</sup> : 2.32 (1.61, 3.34)<br>>16.9 µg/m <sup>3</sup> : 2.51 (1.73, 3.64) |

OR = odds ratio.

†Study published since the 2009 PM ISA.

#### 5.1.10.4.2 Temperature

Instead of conducting traditional seasonal analyses, some recent studies examined whether there was evidence that higher temperatures modified the relationship between short-term PM<sub>2.5</sub> exposure and asthma hospital admissions and respiratory mortality. Cheng et al. (2015) examined whether specific temperatures modified the PM<sub>2.5</sub>-asthma hospital admission association in Kaohsiung, Taiwan. The authors reported that PM<sub>2.5</sub> associations were larger in magnitude when analyses were restricted to days with lower temperatures, 13–25°C (RR = 1.10 [95% CI: 1.06, 1.13]) compared to days with higher temperatures (i.e., >25°C: RR = 1.02 [95% CI: 0.98, 1.06]).

Pascal et al. (2014) examined the impact of temperature on the PM<sub>2.5</sub>-respiratory mortality relationship across nine French cities by comparing associations on warm and nonwarm days where warm days were defined as those days where the mean temperature exceed the 97.5th percentile of the mean temperature distribution. Pascal et al. (2014) reported no evidence of an interaction between PM<sub>2.5</sub> and warm days on respiratory mortality.

Additional studies conducted in Asia, although at higher mean PM<sub>2.5</sub> concentrations (i.e., in many cases >20 µg/m<sup>3</sup>), also examined whether high temperatures modify the PM<sub>2.5</sub>-respiratory mortality relationship. Li et al. (2015b) examined whether same-day temperature, either higher (>23.5°C) or lower temperatures (<2.6°C), modifies the PM<sub>2.5</sub>-respiratory mortality relationship at lag 0 and 1. At lag 0, there was evidence of an association larger in magnitude at high temperatures (1.7% [95% CI: 0.92, 3.3]) compared to medium (0.76% [95% CI: –0.04, 2.0]), with no evidence of an association at low temperatures. However, at lag 1, the strongest evidence of an association was only for the medium

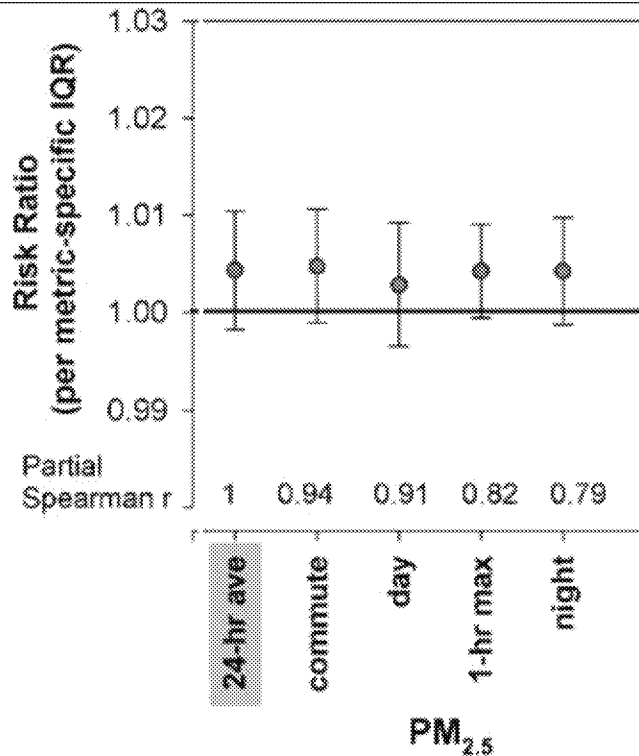
temperatures (0.80% [95% CI: -0.15, 1.8]). Sun et al. (2015) provides evidence contradictory to the results of Li et al. (2015b). At lag 0–1 days, the authors observed positive associations at high ( $\geq 25^{\circ}\text{C}$ ) and medium temperatures, ranging from 0.26–0.39%, but the magnitude of the association was much smaller than that observed for low temperatures ( $< 22^{\circ}\text{C}$ ) (1.2% [95% CI: 0.51, 1.8]). Unlike Li et al. (2015b), Sun et al. (2015) did not specifically focus on the tails of the temperature distribution, which complicates the interpretation of the results between the two studies, especially considering the low temperature category in Sun et al. (2015) is relatively similar to the high temperature category in Li et al. (2015b). Overall, the evidence across studies is inconclusive as to whether specific temperature ranges modify the association between short-term  $\text{PM}_{2.5}$  exposure and respiratory mortality.

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#### 5.1.10.5 Averaging Time of $\text{PM}_{2.5}$ Concentrations

Collectively, the combination of studies evaluated in the 2009 PM ISA and within this section largely support an association between short-term  $\text{PM}_{2.5}$  exposures and increases in respiratory-related hospital admissions and ED visits, specifically when using a 24-hour average  $\text{PM}_{2.5}$  concentration averaging time. To date, very few studies have examined associations with subdaily averaging times for  $\text{PM}_{2.5}$  concentrations (e.g., 1-hour max), with some evidence indicating associations between ED visits and 1-hour max  $\text{PM}_{2.5}$  concentrations. Previously, in Bronx, NY, RRs for asthma ED visits were similar in magnitude for 24-hour average and 1-hour max  $\text{PM}_{2.5}$  concentrations (ATSDR, 2006). The two averaging times were found to be highly correlated ( $r = 0.78$ ), but the spatiotemporal variability of 1-hour max concentrations was not reported. Similarly, other studies that examined subdaily averaging times have not provided information on the spatiotemporal variability of other exposure metrics, such as 3-hour average or 6-hour average  $\text{PM}_{2.5}$  concentrations, which were examined in studies conducted in six Canadian cities (Stieb et al., 2009) and Seoul, South Korea (Kim et al., 2015). However, in both studies, the authors reported no evidence of an association between 24-hour average  $\text{PM}_{2.5}$  concentrations and asthma ED visits, nor was there evidence of an association using the subdaily averaging times.

Darrow et al. (2011) systematically examined a series of averaging times to assess whether the 24-hour exposure metric was appropriate. The authors examined several subdaily averaging times (i.e., 1-hour max, commute time average [7–10 a.m. and 6–9 p.m.], daytime average [8 a.m.–7 p.m.], and nighttime average [12–6 a.m.]) in addition to the traditional 24-hour average when examining the relationship between short-term  $\text{PM}_{2.5}$  exposure and respiratory-related ED visits. The averaging times were found to be highly correlated with one another with  $r = 0.79\text{--}0.94$ , which is consistent with ATSDR (2006). Across the averaging times examined, the authors reported relatively consistent positive associations of similar magnitude, but confidence intervals were wide (Figure 5-18).



Source: Permission pending, [Darrow et al., \(2011\)](#).

**Figure 5-18 Association between short-term PM<sub>2.5</sub> exposure and respiratory-related emergency department (ED) visits in Atlanta, GA at lag 1 for 24-hour average and subdaily exposure metrics.**

While hospital admission and ED visit studies can examine alternative averaging times for the exposure metric if ambient monitoring data is available, panel studies using personal monitors can examine more refined time scales of exposure but are limited to studies of pulmonary inflammation and lung function. A strength of studies of pulmonary inflammation is examination of the hourly lag structure of PM<sub>2.5</sub> associations. Most ([Barraza-Villarreal et al., 2008](#); [Rabinovitch et al., 2006](#); [Mar et al., 2005](#)) but not all ([Berhane et al., 2011](#)) results show an increase in inflammation with increases in PM<sub>2.5</sub> concentration averaged over the preceding 1 to 11 hours. Additional support is provided by associations with mean personal PM<sub>1.5</sub> exposure in nonhome/school locations ([Rabinovitch et al., 2016](#)). Associations also were observed with 1-hour or 8-hour maximum PM<sub>2.5</sub> that were larger than those for 24-hour average PM<sub>2.5</sub> ([Delfino et al., 2006](#); [Rabinovitch et al., 2006](#)). Maximum concentrations occurred before inflammation was measured. Some results indicate that PM<sub>2.5</sub> exposure may have a rapid and transient effect on pulmonary inflammation in people with asthma. For Seattle, WA and Riverside and Whittier, CA, distributed lag models show an increase in eNO with the 1-hour average PM<sub>2.5</sub> concentration up to 5 or 10 hours prior but not with longer lags of 24–48 hours ([Delfino et al., 2006](#); [Mar et al., 2005](#)). eNO measured at well-defined intervals after a scripted 2-hour exposure during morning commutes increased

3 hours post-exposure (Mirabelli et al., 2015). Longer lags were not examined, and a similar previous study did not observe any changes up to 22 hours after exposure (McCreanor et al., 2007). It is important to note that most recent studies examined 24-hour or multiday average PM<sub>2.5</sub>, which may explain the inconsistency in associations observed (see section on eNO). However, studies evaluated in the 2009 PM ISA also used 24-hour or multiday average PM<sub>2.5</sub> concentrations and reported positive associations (Liu et al., 2009; Allen et al., 2008; Delfino et al., 2006).

Additional studies examined subdaily averaging times through 1 to 8-hour scripted outdoor exposures near pollution sources. Epidemiologic studies of scripted outdoor exposures examined PM<sub>2.5</sub> at high-traffic locations and found inconsistent results with respect to respiratory effects in healthy populations. Among epidemiologic studies of adults commuting by car, bus, or bicycle, working as school crossing guards or traffic police, or spending time in high-traffic areas, PM<sub>2.5</sub> was associated with increases in pulmonary inflammation (Mirowsky et al., 2015; Zhao et al., 2015; Steenhof et al., 2013) or decreases in lung function (Huang et al., 2016; Shakya et al., 2016; Mirabelli et al., 2015; Weichenthal et al., 2011). Effects were not observed in other studies of pulmonary inflammation (Zuurbier et al., 2011a) or lung function decrements (Matt et al., 2016; Zhao et al., 2015; Zuurbier et al., 2011b; Fan et al., 2008). For PM<sub>2.5</sub> exposures of 1–8 hours, no distinct pattern of association or effect is observed by exposure duration or concentration. Among epidemiologic studies in the U.S., Canada, and Europe conducted near traffic or a steel plant, 1- to 8-hour average PM<sub>2.5</sub> concentrations with means 8.1–39 µg/m<sup>3</sup> were linked to respiratory effects in some studies (Mirabelli et al., 2015; Mirowsky et al., 2015; Dales et al., 2013), but not in others (Strak et al., 2012; Weichenthal et al., 2011). Results are inconsistent at concentrations higher than 39 µg/m<sup>3</sup> as well, but associations were observed in traffic police, adults exercising outdoors, or adults exposed in a transport hub (Huang et al., 2016; Shakya et al., 2016; Kesavachandran et al., 2015; Zhao et al., 2015) with mean 2- to 8-hour average PM<sub>2.5</sub> concentrations 53–323 µg/m<sup>3</sup>.

Across the studies evaluated that examined subdaily averaging times and subsequent respiratory effects, the effects tend to be transient. PM<sub>2.5</sub>-associated increases in pulmonary inflammation and oxidative stress (Steenhof et al., 2013; Weichenthal et al., 2011) or decreases in lung function (Mirabelli et al., 2015) often were isolated to immediately or 1 or 2 hours after exposure near traffic, but not 3 to 18 hours after exposure. PM<sub>2.5</sub> exposure while walking near high-traffic roads and in a forest was associated with eNO 24 hours after exposure (Mirowsky et al., 2015), but lung function decreased only immediately after exposure.

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#### 5.1.10.6 Concentration-Response Relationship and Threshold Analyses

At the completion of the 2009 PM ISA, the examination of the PM C-R relationship in epidemiologic studies focused on mortality and cardiovascular outcomes. Recent studies expanded the evaluation of the PM<sub>2.5</sub> C-R relationship to encompass respiratory-related outcomes, including respiratory-related hospital admissions and ED visits with a focus on examining both the shape of the C-R